

**Neurobiological and Neuropsychological Deep Endophenotypes of Behavioral Response
Inhibition: RDoC Empirical and Mathematical AI Feature Engineering**

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JOHN E. WEHRLI

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Mental illness is nothing more than a soup of normal behaviors that, when mixed just so and brought to a boil, result in abnormal behavior . . .

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Abstract

Impulsivity and behavioral response inhibition represent core transdiagnostic constructs in behavioral neuroscience and translational psychiatry, central to ADHD, autism, borderline personality disorder, and schizophrenia. Despite decades of research, the literature fails to adequately characterize cognitive control dimensionality, limiting differential diagnosis and precision psychiatry. This quantitative Research Domain Criteria (RDoC) study discriminated and dimensionalized neurobiological and neuropsychological endophenotypes through deep phenotyping, guided by Barkley's inhibitory deficit theory, to enable computational neuroscience applications. 480 adults (of 6,603 participants) completed the Barratt Impulsiveness Scale (BIS-11), Wisconsin Card Sorting Test (WCST), Go/No-Go Task (GNG), and Stop Signal Task (SST). Participants were dichotomized into high and low trait motor impulsivity (MI) groups. MANOVA examined group differences across nine cognitive control variables. Cook's influential outlier analysis enhanced statistical power, while cross-model convergent analysis identified optimal deep endophenotype combinations for artificial intelligence (AI) machine learning feature engineering. Results demonstrated significant multivariate WCST effects, $p = .009$, partial $\eta^2 = .024$, with marginal significance after influential outlier removal, $p = .063$, partial $\eta^2 = .018$; significant multivariate GNG effects, $p = .008$, partial $\eta^2 = .028$, with practically significant SST effects, $p = .019$, partial $\eta^2 = .024$. Cross-model convergent analysis identified three optimal decomposed endophenotype candidates (WCST non-perseverative errors [NPE], GNG commission errors [CE], SST stop signal reaction time [SSRT]) for discriminating MI groups, $p < .001$, partial $\eta^2 = .040$. A reaction time threshold discovery revealed high MI individuals achieve optimal GNG CE minimization significantly faster (558ms/high-MI vs. 625ms/low-MI), challenging conventional intervention approaches by suggesting strategies

based on speed-accuracy optimization. WCST findings also discriminated motor and choice impulsivity subtypes through preserved perseverative responses (PR), suggesting intact caudate nucleus function while revealing MI-specific prefrontal dysfunction. This computational and behavioral neuroscience study successfully validated deep decomposed endophenotype candidates, resolving measurement problems in impulsivity research, providing empirical support for RDoC latent variable approaches. Findings enable neurocomputational modeling applications including machine learning, deep learning, and digital twins for behavioral phenotype assessment in computational psychiatry. Future research should validate these endophenotype (neurophenotype) candidates across independent samples, expand to genetic and neuroimaging studies, and develop neurocomputational AI models for personalized psychiatric interventions.

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“All models are wrong, some are useful.” – George Box

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“The task is not to see what has never been seen before, but to think what has never been thought before about what you see everyday.” - Erwin Schrodinger

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Chapter 1: Introduction

Behavior is the phenotypic output of the brain and connotes observable action.

Impulsivity, as action, can be defined as behavior without forethought (Fornaro et al., 2024; Strickland & Johnson, 2021). It is a multifaceted construct characterized by suboptimal action without due consideration of negative consequences (Crisp & Grant, 2024; Pan et al., 2020; Stahl et al., 2014, Strickland & Johnson, 2021). It is also transdiagnostic in that it is a core symptom of numerous DSM disorders including ADHD, borderline personality disorder, schizophrenia, and autism (Crisp & Grant, 2024; Fornaro et al., 2024; Friedman & Miyake, 2004; Lombardo et al., 2023; Mitolo et al., 2024; Stahl et al., 2014; Waite, et al., 2024; Wang et al., 2024).

Consequently, impulsivity is considered an important and relevant construct in abnormal psychology and a warranted putative endophenotype under the research domain criteria (RDoC) in behavioral neuroscience (Crisp & Grant, 2024; Deng et al., 2023; Fornaro et al., 2024; Mosconi et al., 2023; NIMH, 2021; Strickland & Johnson, 2021).

Although often treated as unitary, impulsivity has been divided into two or more facets in the literature. For example, trait impulsivity refers to an enduring stable personality trait and state impulsivity refers to premature ephemeral dysregulated responses to internal and external stimuli (Buhler et al., 2023; Dewi et al., 2023; Pan et al., 2020). Neuropsychological measures of trait impulsivity are typically self-report measures, such as the Barratt Impulsiveness Scale (BIS-11), whereas those of state impulsivity are typically laboratory behavioral measures, such as the go/no-go and stop signal tasks (Crisp & Grant, 2024; Pan et al., 2020). Impulsivity has been further divided into three to five or more facets, such as impulsive action and impulsive choice and impulsive personality (i.e., trait impulsivity; Deng et al., 2023; MacKillop et al., 2016; Rogers et al., 2021; Stahl et al., 2014).

Impulsive action can result from the inability to inhibit a motor response— that is, disinhibition or lack of impulse control (Rogers et al., 2021). Disinhibition or lack of impulse control implicates a facet of impulsivity termed behavioral response inhibition (BRI), which itself is a multifaceted, not unitary, construct and putative endophenotype of its own (Ettinger et al., 2018; Saracaydin et al., 2024; Xia et al., 2024). Three facets of BRI include interference control (which can be associated with impulsive choice), prepotent response inhibition (the ability to suppress a primed prepotent response to a stimulus), and prepotent response extinction, terminology used for the purposes of this study to represent the ability to extinguish an on-going response to a stimulus after it is no longer optimal to continue responding (Ettinger et al., 2018; Saracaydin et al., 2024). The last two facets are associated with impulsive action, which implicates motor trait impulsivity and motor inhibition and were thus relevant and warranted putative endophenotypes under this study.

Endophenotypes

Endophenotypes come from psychiatric genetics and are intermediate or mediational phenotypes (the observable or measurable products of genotypes) along the path between genotype and behavioral phenotype (Gottesman & Gould, 2003; Gray et al., 2018; Iacono, 2018; Mosconi et al., 2023). The modern embodiment of endophenotypes is that of latent (hidden, non-apparent or non-obvious) variables that comprise mediational phenotypes that can, nonetheless, be quantitatively measured by proxy and used in the etiological inquiry of the path from genotype to behavioral phenotype (Gottesman & Gould, 2003; Jonas & Markon, 2014; Mosconi et al., 2023). Consequently, one way to think about endophenotypes is in the context of their units of measure or units of analysis (see RDoC discussion below; Mosconi et al., 2023). In that respect, they can manifest as measurable traits or characteristics via neuropsychological

measures or subscales of measures (neuropsychological endophenotypes), and biological and neurobiological phenomena via neuroimaging and neurophysiological measures (neurobiological endophenotypes), provided that, at a minimum, each has strong genetic etiology and liability (Jonas & Markon, 2014; Mosconi et al., 2023).

For example, the psychological constructs of anxiety and impulsivity, and their facets, cannot be measured directly (they are latent variables), but can be measured operationally through self-report or laboratory behavioral instruments (neuropsychological measures), and neuroimaging and neurophysiological instruments. Neuropsychological and neurobiological measures can be candidate endophenotypes in their own right, in that they are direct observable measures that represent latent variables that have direct effects on them. Although the literature often refers to a psychological construct, or a facet of a psychological construct, as a candidate endophenotype for behavioral phenotypes, it is the measures that operationalize it and its facets and so can be viewed as endophenotypes as well (see Demetriou et al., 2019; Jonas & Markon, 2014; Mosconi et al., 2023). Viewing measures as endophenotypes may be useful for two reasons. First, the literature often erroneously treats multidimensional psychological constructs as unitary, and much of the literature that doesn't, treats facets of psychological constructs as unitary. Second, the literature erroneously assumes that neuropsychological instruments (units of measure or analysis) measure unitary constructs or are indifferent (agnostic) to their facets.

Behavioral phenotypes include mental disorders, which are polygenic (having more than one risk [susceptibility] gene) and heterogenic in that many mutations or variants (polymorphisms or alleles) of risk genes contribute to the risk (liability) of a particular mental disorder (behavioral phenotype; Iacono, 2018; Mosconi et al., 2023). Studies of risk alleles typically find small effect size for given alleles, resulting in weak, contradictory, or poorly

reproducible liability imposed by such alleles on behavioral phenotypes (Doyle et al., 2005; Iacono, 2018; Smoller, 2019, Umesh & Nizamie, 2014). However, because endophenotypes are closer to the genetic origins of behavioral phenotypes, they should be simpler, less polygenic, and more tightly associated to their genotypes than downstream behavioral phenotypes (Gray et al., 2018; Iacono, 2018). Consequently, neurobiological endophenotypes should be more strongly linked to genotype than neuropsychological endophenotypes, which, in turn should be more strongly linked than behavioral phenotypes (Jonas & Markon, 2014). In other words, the closer to genotype the fewer risk alleles that can be the focus of study, each with progressively larger effect sizes (Iacono, 2018).

The less polygenic characteristic of endophenotypes and their tighter association to genotypes than behavioral phenotypes also means that a given endophenotype can lie in the path between its stronger genotype for that endophenotype, and multiple behavioral phenotypes, meaning endophenotypes are transdiagnostic (Iacono, 2018). Put another way, endophenotypes are indifferent (agnostic) to mental disorder so can be studied in neurotypical, non-clinical populations. Consequently, studying endophenotypes is of practical importance to not only improve the study of the biological (here genetic) correlates of behavioral phenotypes, but to also inform differential diagnosis of those behavioral phenotypes (mental disorders). Yet, after many years in the literature, the endophenotype hypothesis, as it is called, has failed to live up to expectations, with candidate endophenotypes often falling short of the criteria upon which they rely (Jonas & Markon, 2014; Walters & Owen, 2007). Consequently, the study of endophenotypes also has theoretical importance in that it can inform the endophenotype hypothesis and empirical importance because it can help identify valid endophenotypes under the Research Domain Criteria (RDoC), described further below.

The topic of endophenotypes of impulsivity, and BRI in particular, is of practical importance because, as mentioned above, they are core symptoms in many DSM mental disorders. It is of empirical importance because it can improve the predictive power of differential diagnosis of mental disorders that share those symptoms. It is of theoretical importance because it can inform Barkley's theory of inhibitory deficits, which posits that proper engagement of behavioral response inhibition is critical to healthy executive functions (Barkley, 2016). One way to address the limited success of endophenotype research is to select stronger more distinct endophenotypes through improved measurement and dimensionality of the latent variables (psychological constructs) they represent, a process that, for the purposes of this study, was referred to as RDoC latent variable endophenotype decomposition, applying the conceptual framework of the RDoC, which focuses units of measure or analysis and subscribes to the endophenotype hypothesis.

Decomposed endophenotypes can then be used in deep phenotyping (and deep endophenotyping) and empirical and mathematical preprocessing feature selection and feature engineering for neurocomputational models, including models of impulsivity and BRI and models (digital twins) of the four behavioral phenotypes of this study. Neurocomputational models of DSM behavioral phenotypes (comprising deep phenotypes and deep endophenotypes), for example, are built using artificial intelligence (AI) machine learning (ML) and deep learning (DL) tools to create psychiatric disease models to directly inform differential diagnosis and the development of personalized behavioral and psychopharmacological interventions (treatments) for what are really multifactorial dimensional states and phases of psychiatric diseases (Tai et al., 2019). Neurocomputational models can bridge the gap between DSM nomological categories of heterogeneous symptoms that do not map onto their neurobiological substrates and underlying

RDoC enabled domains and units of measure comprising deep phenotypes and deep endophenotypes that do.

Statement of the Problem

The problem addressed in this study was that the endophenotype literature does not adequately characterize and segregate the dimensionality of the latent psychological constructs of impulsivity and impulse control (i.e., behavioral response inhibition [BRI]). The imprecise characterization of impulsivity and BRI has resulted in poor correlation between them and their neuropsychological and neurobiological measures (Strickland & Johnson, 2021), including between their self-report and behavioral measures (Ellingson et al., 2018). The literature has often failed to distinguish among facets (components, features, and factors) of impulsivity and BRI, and which neuropsychological measures (Cogden, 2014; Demetriou, 2018; Korolczuk, 2018), and which neurobiological measures (Bong et al., 2020; Skippen et al., 2020) best measure those facets. More specifically, the literature has failed to test whether subscales of self-report measures are better correlated with subscales of behavioral measures than higher order scales are (Friedman & Miyake, 2004; Raud et al., 2020; Stahl et al., 2014). Consequently, researchers are unable to consistently and reliably differentially map facets of impulsivity and BRI (Ellingson et al., 2018; Fortgang et al., 2016; Sperl et al., 2021). As a result of these failures, impulsivity has been questioned as a psychological construct (Strickland & Johnson, 2021), and both impulsivity and BRI have largely failed to meet their potential as putative endophenotypes (Jonas & Markon, 2014). While it is clear that both impulsivity and deficits in BRI are the most common symptoms across many DSM disorders and each is a multidimensional, and not unitary, construct, it remains unclear whether they or their facets qualify as valid endophenotypes. The negative consequences of not addressing the need to consistently characterize and segregate the

dimensionality of impulsivity and BRI include both failure of reliable differential diagnosis among clinicians, and failure of studies of genetic and neurobiological correlates of both impulsivity and its behavioral phenotypes to produce sound, consistent results (Sanislow et al., 2019). Poorly characterized, segregated, and dimensionalized facets of impulsivity and BRI can also result in poor and weak feature selection, feature extraction, and feature engineering for neurocomputational predictive, generative, or causal AI models comprising deep phenotypes of behavioral phenotypes or behavioral constructs, which can undermine a goal in computational psychiatry to use AI to inform differential diagnosis and treatment (Brucar et al., 2023; Erguzel et al., 2015; Huys et al., 2016; Pauli & Lockwood, 2023; Stephan & Mathys, 2014).

Purpose of the Study

The purpose of this quantitative quasi-experimental ex post facto study was to discriminate neurobiological and neuropsychological measures through assessing the relationships between subscales of the Barratt Impulsiveness Scale (BIS-11) for low and high trait motor impulsivity and subscales of three laboratory behavioral measures of BRI, the go/no-go task (GNG), stop signal task (SST), and Wisconsin card sorting test (WCST). This study was a logical, explicit response to the problem of the endophenotype literature's failure to adequately characterize and segregate the dimensionality of impulsivity and BRI. The study examined the differences among three dependent outcome variables comprising lower order subscales (three subscales per measure) of each of the three laboratory behavioral measures and an independent dichotomous predictor variable comprising high and low trait motor impulsivity as measured by the BIS-11 psychometric self-report measure.

The initial target population under study was adult neurotypical males ages 18-34, but, as explained in Chapter 4, it was later changed to adult neurotypical males and females ages 18-40.

The study used purposive non-probability convenience sampling from the Qualtrics panel of United States participants (subject to exclusion criteria). G*Power version 3.1.9.7 (March 2020) was used to calculate the sample size using the F tests test family, MANOVA Global effects (for linear composites of two or more dependent variables), for an *a priori* power analysis for two groups and three response variables for each of the three studies and an alpha of .05 (Faul et al., 2007, 2009). The power analysis generated a preliminary minimum sample size of 280 for an actual power of .95 (560 for upper and lower quartile groupings). Because there were multiple dependent variables and dichotomous predictor variables comprising two groups, one-way (one-factor) between subjects unpaired multivariate analysis of variance (MANOVA) was used to assess the differences among composite means of linear variates of a set of psychometric measures comprising dependent outcome variables from each instrument for each level for each study with post-hoc independent sample t -tests (or Welch's test) conducted if results were statistically significant to identify the source of the differences and thus, to identify novel decomposed endophenotypes (Schumacker & Lomax, 2010). Quadratic regression was used to discover a novel reaction time threshold for optimal speed-accuracy minimization of commission errors (CE) in the GNG model. Cook's leverage-residual (influence) sensitivity analysis was used to improve statistical power and test model robustness. Cross-model convergent analysis was used to identify frameworks of combined deep endophenotypes to improve predictive power across all models and identify the optimal power-parsimony combination of features for AI applications. These decomposed endophenotypes can then be used in deep phenotyping (and deep endophenotyping) as preprocessed mathematically and empirically selected features for neurocomputational models of behavioral phenotypes in computational psychiatry.

Introduction to Theoretical Framework

This study integrated two conceptual and theoretical frameworks, the Research Domain Criteria (RDoC) developed by the National Institutes of Mental Health (NIMH), which subscribes to the endophenotype hypothesis, and Barkley's theory of inhibitory deficits (Barkley, 1997a; Barkley, 1999), which can be used to frame impulsivity and BRI as RDoC endophenotypes. The RDoC frames endophenotype research using psychological constructs, such as impulsivity, seeking to improve the dimensionality of those constructs, and subscribes to the endophenotype hypothesis. That is, lower order mediators, such as impulsivity (symptoms or endophenotypes), of behavioral phenotypes (mental disorders), may better map onto neurobiological correlates than onto the more complex DSM behavioral phenotypes, which are syndromal aggregates of symptoms (Kozak & Cuthbert, 2016). Thus, underlying the RDoC is the previously described premise that endophenotypes are better targets for research to understand the connection between neurobiological correlates and behavioral phenotypes. The RDoC is a framework from which to design and conduct research based on a matrix of neurobiological and neuropsychological measures (units of analysis) and behavior (psychological domains, constructs, and subconstructs) that can be observed (Kozak & Cuthbert, 2016). The RDoC matrix may enable the encoding of unique, sensitive and selective scale agnostic multimodal differential deep phenotypes (and deep endophenotypes) of putative polygenic, multifactorial, and heterogeneous behavioral phenotypes and used to train dynamic neurocomputational predictive and diagnostic AI models and digital twins of psychiatric disorders (Delude, 2015; Gershon et al., 2018).

The RDoC was developed to address a disconnect between research findings from molecular and psychiatric genetics studies and neuroscience studies that use neuroimaging, for

example, and DSM categorical mental disorders (behavioral phenotypes; Kozak & Cuthbert, 2016). The failure of genetics and neuroscience research to map onto the DSM nosology points to the square peg and round hole challenge of merging two different conceptual frameworks, the transdiagnostic nature of molecular genetics and neuroscience and diagnostic categories of the DSM. The RDoC attempts to reconcile an apparently false premise in the literature, that categorical DSM mental disorders (behavioral phenotypes) are unitary constructs with unique pathophysiology and psychopathology that can be tied to specific unique neurobiological etiology (Kozak & Cuthbert, 2016). Thus, RDoC studies are DSM agnostic. The research questions of this RDoC study are intended to inform the identification of better discriminated and segregated measures (RDoC units of analysis) that can comprise DSM agnostic stronger candidate endophenotypes related to BRI to both expand Barkley's theory of inhibitory deficits (described below) to other behavioral phenotypes that share the same endophenotypes and inform the RDoC psychological domains and constructs related to impulsivity. In the case of this study, such segregation and discrimination was a product of latent variable endophenotype decomposition to identify deep endophenotypes to load onto deep phenotypes of subtypes of behavioral phenotypes.

The theoretical framework that was used here to frame the relevance of measures of BRI as endophenotypes for impulsivity related traits, characteristics, behaviors, and behavioral phenotypes, as linked to neurobiological correlates, is Barkley's theory of inhibitory deficits. Barkley (1997a, 1999) proposed a unifying theory for ADHD that posited that deficits in inhibitory control (impulse control) are central to this behavioral phenotype. The theory parses three facets of BRI, (a) prepotent response inhibition, which comprises inhibition of a response that is subject to the availability of immediate positive or negative reinforcement or for which

such reinforcement has been primed through conditioning, (b) inhibition (extinction) of an ongoing response that has already begun, and (c) maintenance of the inhibitory process (Barkley, 1997a; Barkley, 1997b; Barkley, 1997c; Barkley, 1999). Thus, the two frameworks are naturally interrelated and were mutually complementary to address the problem, purpose, and research questions.

The frameworks provided an understanding of the problem because a key goal of the RDoC is to better discriminate psychological constructs and Barkley's theory suggests discriminate components of BRI that can be tested, measured, and better discriminated. The frameworks supported the development the purpose because the measures are among the units of analysis across several levels of the RDoC and are implicated in discriminating the facets of BRI under Barkley's theory. The frameworks provided a lens by which to answer the research questions by both providing a framework to identify discriminating deep endophenotypes and improving the application of Barkley's theory across behavioral phenotypes.

Introduction to Research Methodology and Design

This quantitative quasi-experimental ex post facto study was designed to discriminate neurobiological and neuropsychological measures by examining the differences among three dependent outcome variables comprising lower order subscales (three subscales per measure) of each of three laboratory behavioral measures (the go/no-go task [GNG], stop signal task [SST], and Wisconsin card sorting test [WCST]) and an independent dichotomous predictor variable comprising high and low trait motor impulsivity as measured by the BIS-11 psychometric self-report measure. This study was quasi-experimental because associations for study were empirically measured, but not all confounding variables were controlled; some were latent, and both sampling and group assignment was not random (Leedy & Ormrod, 2013; Shadish et al.,

2002). It was ex post facto because each subject was exposed to an ex post facto pretest condition of dichotomous outcome measures (Leedy & Ormrod, 2013; Shadish et al., 2002).

A quantitative quasi-experimental ex post facto study was appropriate for understanding the problem, which was that the endophenotype literature does not adequately characterize and segregate the dimensionality impulsivity and BRI, because the measures were quantitative and discrimination required pretest groupings. A quantitative quasi-experimental ex post facto study was appropriate for addressing the purpose, which was to discriminate neurobiological and neuropsychological measures through assessing the relationships between subscales of the BIS-11 self-report measure and subscales of three laboratory behavioral measures of BRI (GNG, SST, WCST), because it bifurcated the groups as independent predictor variables and quantified the measures to be discriminated against those groups. A quantitative quasi-experimental ex post facto study was appropriate for answering the research questions, which asked whether the selected composite subscales of each measure discriminated high and low motor impulsiveness and then sought to identify the most significant discriminating variable for each measure, because composites of dependent variables lend themselves to MANOVA analysis.

The study used purposive non-probability convenience sampling of volunteer male and female participants 18-40 (originally intended to be limited to male participants 18-34) recruited through Qualtrics. Per the aforementioned power analysis, 280 was the minimum number of participants needed to achieve statistical significance. However, to ensure a sufficient number to bifurcate groups and account for potential attrition, the study targeted about 600 participants. Each potential participant was pre-screened for exclusion criteria (under 18 or over 40 [originally over 34, and females], left-handed, non-normal vision, color blindness, poor hearing, and non-English proficiency) and those that were not excluded completed informed consent. After

verification of informed consent, participants were then administered an additional comprehensive screening questionnaire and all psychometric self-report and laboratory behavioral measures in one sitting via Qualtrics on-line using a unique link to a portal hosting the Inquisit 6 Web data collection suite provided by Millisecond Software, (Seattle, Washington). The following were used for each subject: For the BIS-11, total and motor impulsiveness Factor I and Factor II subscale scores. For GNG, mean reaction time (mRT) as well as number of commission errors (CE) and number of omission errors (OE). For the SST, stop signal reaction time (SSRT) as well as number of commission errors and number of omission errors. For the WCST, preservative responses (PR), non-preservative errors (NPE), and failure to maintain set (FMS).

As previously discussed, the use of multiple dependent variables and dichotomous predictor variables, comprising two groups, supported use of one-way (one-factor) between subjects unpaired multivariate analysis of variance (MANOVA) to assess the differences among composite means of linear variates of a set of laboratory behavioral measures comprising dependent outcome variables from each instrument for each level for each study with post-hoc independent sample *t*-tests (or Welch's test) conducted to identify the source of the differences and, thus, to identify novel decomposed endophenotypes (Schumacker & Lomax, 2010).

Research Questions

The research questions are presented next along with associated hypotheses. Each primary research question corresponds to one of the laboratory behavioral measures (one model) of this study, which correspond to RDoC units of analysis. Each question has three sub-questions to support post hoc analysis of each dependent variable.

RQ1

Do linear variates of perseverative responses (PR), non-perseverative errors (NPE), and failure to maintain set (FMS) measures on the Wisconsin Card Sorting test (WCST) differ between high and low trait motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults ages 18-40?

RQ1a. Is there a difference in perseverative responses (PR) in the WCST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40?

RQ1b. Is there a difference in non-perseverative errors (NPE) in the WCST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults 18-40?

RQ1c. Is there a difference in failure to maintain set (FMS) measures in the WCST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40?

RQ2

Do linear variates of mean reaction time (mRt), commission errors (CE), and omission errors (OE) in the go/no-go (GNG) task differ between high and low trait motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults ages 18-40?

RQ2a. Is there a difference in mean reaction time (mRt) in the GNG task between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40?

RQ2b. Is there a difference in commission errors (CE) in the GNG task between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults 18-40?

RQ2c. Is there a difference in omission errors (OE) in the GNG task between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults 18-40?

RQ3

Do linear variates of stop signal reaction time (SSRT), commission errors (CE), and omission errors (OE) in the stop-signal task (SST) differ between high and low trait motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults ages 18-40?

RQ3a. Is there a difference in stop signal reaction time (SSRT) in the SST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40?

RQ3b. Is there a difference in commission errors (CE) in the SST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40?

RQ3c. Is there a difference in omission errors (OE) in the SST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40?

Hypotheses***H1₀***

Linear variates of perseverative responses (PR), non-perseverative errors (NPE), and failure to main set (FMS) measures on the Wisconsin Card Sorting test (WCST) do not differ between high and low trait motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults ages 18-40.

H1_a

Linear variates of perseverative responses (PR), non-perseverative errors (NPE), and failure to main set (FMS) measures on the Wisconsin Card Sorting test (WCST) differ between high and low trait motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults ages 18-40.

H1a₀. There is no difference in perseverative responses (PR) in the WCST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H1aA. There is a difference in perseverative responses (PR) in the WCST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H1b0. There is no difference in non-perseverative errors (NPE) in the WCST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H1bA. There is a difference in non-perseverative errors (NPE) in the WCST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H1c0. There is no difference in failure to maintain set (FMS) measures in the WCST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H1cA. There is a difference in failure to maintain set (FMS) measures in the WCST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H2₀

Linear variates of mean reaction time (mRT), commission errors (CE), and omission errors (OE) in the go/no-go (GNG) task do not differ between high and low trait motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults ages 18-40.

H2_a

Linear variates of mean reaction time (mRT), commission errors (CE), and omission errors (OE) in the go/no-go (GNG) task differ between high and low trait motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults ages 18-40.

H2a0. There is no difference in mean reaction time (mRt) in the GNG task between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H2aA. There is a difference in mean reaction time (mRt) in the GNG task between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H2b0. There is no difference in commission errors (CE) in the GNG task between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H2bA. There is a difference in commission errors (CE) in the GNG task between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H2c0. There is no difference in omission errors (OE) in the GNG task between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H2cA. There is a difference in omission errors (OE) in the GNG task between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H3₀

Linear variates of stop signal reaction time (SSRT), commission errors (CE), and omission errors (OE) in the stop-signal task (SST) do not differ between high and low trait motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults ages 18-40.

H3_a

Linear variates of stop signal reaction time (SSRT), commission errors (CE), and omission errors (OE) in the stop-signal task (SST) differ between high and low trait motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adult males ages 18-40.

H3a0. There is no difference in stop signal reaction time (SSRT) in the SST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H3aA. There is a difference in stop signal reaction time (SSRT) in the SST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H3b₀. There is no difference in commission errors (CE) in the SST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H3b_A. There is a difference in commission errors (CE) in the SST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H3c₀. There is no difference in omission errors (OE) in the SST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H3c_A. There is a difference in omission errors (OE) in the SST between high and low trait motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

Significance of the Study

This study contributed to the field of study and advanced the literature by identifying at least one valid endophenotype of BRI that can be discriminated and segregated across its facets differentially and map as or onto deep endophenotypes. As described above, numerous problem methodological, empirical, and knowledge gaps exist in the literature. First, lower order facets of BRI are inconsistently measured by both distinct neuropsychological measures and subscales of those measures to identify more suitable candidate endophenotypes via stronger links to neurobiological correlates and/or behavioral phenotypes. Second, task measures inconsistently discriminate facets, so measures of neurobiological endophenotypes do not differentially map those facets consistently and reliably. Third, since tasks inconsistently discriminate facets, they also fail to consistently differentially map onto behavioral phenotypes, if at all. Fourth, the literature has failed to test (or discriminate) whether subscales of self-report measures are better correlated with subscales of behavioral measures than higher order scales (factors) are. This final gap ties to previously described poor correlation between self-report and behavioral measures in

the literature. This study aimed, in part, to inquire whether deep endophenotyping can demonstrate better correlations.

This study was significant in that it aimed to address these gaps and advance the guiding frameworks of the RDoC and Barkley's theory of inhibitory deficits. Better discriminating key task measures of BRI is important to improve specific units of analysis in the RDoC related to impulsivity/BRI by improving the construct and discriminate validity of subscale measures, which in turn can add layers of deep endophenotypes to improve resolution of deep phenotypes of behavioral phenotypes. For example, while the literature has improved the construct validity of neuropsychological instruments by identifying particular instruments best suited to particular constructs, it has done far less to identify instrument scales and subscales that dimensionalize those constructs. Consequently, if one can improve the construct validity of a neuropsychological measure in the context of its ability to measure a facet of a broader construct, even if that compromises its content validity on the broader construct, it may be possible to better discriminate the genetic liability of the facet and both improve its candidate endophenotype status and uncover deep endophenotypes as a product of the improved resolution of better discrimination.

Essentially, this approach to addressing the problem stated above would seek to develop a nomological network of the dimensions of motor impulsivity as a latent variable through observational sub-measures that segregate those dimensions, a process referred for the purposes of this study as RDoC latent variable endophenotype decomposition, a process of deep endophenotyping. Finally, better characterized, segregated, and dimensionalized facets of impulsivity and BRI can improve feature selection, feature extraction, and feature engineering (inputs) for explainable neurocomputational predictive, generative, or causal AI models, digital

twins, and deep phenotypes of behavioral phenotypes or behavioral constructs in computational psychiatry, resulting in better outputs to inform differential diagnosis, precision psychiatry and treatment.

Definitions of Key Terms

Allele

An allele is a variant or version of a particular gene that occurs by token of mutations (polymorphisms) consequential of evolutionary adaptation and natural selection (Knopik, et al., 2017).

Behavioral Genetics

The study of the effect of genetic variation on phenotypes of human behavior (behavioral phenotypes; Knopik et al., 2017)

Behavioral Phenotype

A pattern of observable behavior associated with a biological disorder, including a psychiatric disorder (O'Brien & Yule, 1995).

Biomarker

A measurable objective characteristic or state that is indicative of normal or pathological biological function (Strimbu & Tavel, 2010).

Computational and Behavioral Neuroscience

A branch of computational neuroscience that concerns the development of neurocomputational models of the neurobiological substrates of behavior or of behavioral systems with a neurobiological nexus (Anderson, 2014; Florez, 2012; Moustafa, 2018; Wilson & Collins, 2019).

Computational Neuroscience

A branch of neuroscience that deploys computational algorithms (including via the use of artificial intelligence machine learning and deep learning) to solve, validate, fit, and dynamically iterate complex mathematical and statistical models in computer simulations, which can be representative of current states or predictive of future states (Anastasio, 2010; Anderson, 2014; De Schutter, 2010; Liu & Li, 2024; Mallot, 2013; Miller, 2018; Sanchez, 2021; Stephan et al., 2008; Sterratt et al., 2024; Trappenberg, 2010).

Computational Psychiatry

The application of computational neuroscience, including computational and behavioral neuroscience, to DSM mental disorders (psychopathology; Anticevic & Murray, 2018; Brucar et al., 2023; Fineberg et al., 2017; Friston, 2023; Iglesias et al., 2017; Karvelis et al., 2023; Khaleghi et al., 2022; Montague et al., 2012; Pauli & Lockwood, 2023; Petzschnner et al., 2017; Redish & Gordon, 2016; Series, 2020; Stephan & Mathys, 2014; Wang & Krystal, 2014).

Computational Psychology

The application of computational neuroscience to the operational embodiments of neural circuits and neural network systems in the form of cognition and behavior (Bartlett et al., 2023; Gheibi et al., 2023; Sun, 2008).

Deep Endophenotyping

For the purposes of this study, deep endophenotyping is a process of identifying distinct endophenotypes by decomposing a higher order endophenotype into its facets, factors, features, subtypes, and components, that can each be considered stand along endophenotypes in their own right.

Deep Phenotyping

For the purposes of this study, deep phenotyping is a process of identifying distinct phenotypes, including endophenotypes, along RDoC's scale agnostic units of analysis, domains, and constructs that, in combination, comprise a behavioral phenotype, whether at the population level or at the individual level.

Endophenotype

An endophenotype is an intermediate or mediational phenotype that lies along the path between genotype and behavioral phenotype (Gottesman & Gould, 2003; Gray et al., 2018; Iacono, 2018).

Epigenetics

Epigenetics is the study of heritable variations to a given phenotype that are not the product of genetic polymorphisms and result from interactions between an allele and cellular and environmental mediators that alter the gene's expression (Ellenbroek, 2016).

Feature

A term used in machine learning to represent independent, dependent, intermediate, and floating variables used to build or train machine learning models (Built In., 2024; Guyon & Elisseeff, 2003; Hastie et al., 2009; James et al., 2021; Janssen et al., 2018).

Feature Engineering

The selection (including from feature selection methods), manipulation, and mathematical transformation of variables (raw data) into, and extraction of, features that can be optimally and efficiently incorporated into machine learning models (Built In., 2024; Hastie et al., 2009). Feature engineering includes feature selection and feature extraction.

Feature Extraction

The derivation or extraction of features (via dimensional reduction or mathematical transforms) that most contribute to variation in a system, including features that can be extracted from targets (dependent variables), comprising noise, that features fail to predict (Bishop, 2006; Guyon & Elisseeff, 2006; Hastie et al., 2009; Janssen et al., 2018).

Feature Selection

The process of selecting a subset of variables that most strongly and efficiently (computationally) contribute to building a good predictor for machine learning, including via wrapper methods (scoring of feature subsets via learning), embedded methods (feature selection during training), and filter methods (preprocessing approaches; Guyon & Elisseeff, 2003; Hastie et al., 2009; James et al., 2021).

Genotype

A genotype is the assembly (complete or partial) of an individual's alleles (Knopik et al., 2017).

Heritability

The fraction of variation (differences) of phenotypes that is explained by the variation of genotypes (Mayhew & Meyre, 2017; Zaitlen & Kraft, 2013),

Mathematical Neuroscience

Theoretical neuroscience that uses complex mathematical and statistical models to formulate theoretical abstractions of dynamical neural network systems in the brain across spatiotemporal RDoC scales, from the molecular level, to the synapse, to the neuron, to neural circuits (projections), to entire neural network systems (Anderson, 2014; De Schutter, 2010;

Khaleghi et al., 2022; Liu & Li, 2024; Mallot, 2013; Miller, 2018; Sanchez, 2021; Sterratt et al., 2024; Trappenberg, 2010).

Phenotype

A phenotype is the observable manifestation, product, or expression of a genotype (i.e., morphology, heritable traits, or characteristics) in combination with environmental epigenetic factors. (de Vienne, 2022)

Phylogenetic(s)

The study of evolutionary relationships of heritable traits, including nucleotide and amino acid sequences and morphology, among and within groups of individuals or species. (Wiley & Lieberman, 2011).

Pleiotropic/Pleiotropy

The concept where a given allele confers risk to multiple phenotypes (de Vienne, 2022; Fisch, 2022; Martin et al., 2019). A phenomenon where a single gene influences two or more phenotypes or phenotypic traits (Stearns, 2010)

Polygenic

A non-Mendelian heritable trait or phenotype that is influenced by two or more genes (Plomin & von Stumm, 2021; Stearns, 2010).

Polymorphism

A genetic polymorphism is a mutation in a sequence of DNA that results in an allele or more than one discontinuous genotype at a locus for a given gene and includes single nucleotide polymorphisms (SNPs), tandem repeats (TRs), and copy number variants (CNVs, Knopik et al., 2017).

Psychiatric Genetics

A subfield of behavioral genetics that focuses on role of genetics in behavioral phenotypes comprising mental disorders (Schulze & McMahon, 2018).

Terms introduced by this dissertation

Prepotent Response Extinction, Deep Endophenotyping, Endophenotype Decomposition, Monogenic Decomposition.

Summary

This chapter presented an overview of the background and methodological design of a quantitative quasi-experimental ex post facto study examining relationships between trait motor impulsivity on the BIS-11 and three laboratory behavioral measures of behavioral response inhibition (BRI). Impulsive action can be defined as behavior without forethought (Fornaro et al., 2024; Strickland & Johnson, 2021). It is a core symptom of a plurality of mental disorders, including ADHD, autism, borderline personality disorder, and schizophrenia (Crisp & Grant, 2024; Friedman & Miyake, 2004; Fornaro et al., 2024; Lombardo et al., 2023; Mitolo et al., 2024; Stahl et al., 2014; Waite, et al., 2024; Wang et al., 2024). Consequently, it is an important construct in abnormal psychology and putative endophenotype under the RDoC, appearing under two domains in the RDoC matrix.

Endophenotypes are intermediate or mediational phenotypes that lie along the path between genotype and behavioral phenotype (mental disorders; Gottesman & Gould, 2003; Gray et al., 2018; Iacono, 2018; Mosconi et al., 2023). They are considered better targets of study for both the etiology and differential diagnosis of behavioral phenotypes. The RDoC was developed to apply the endophenotype hypothesis by focusing on psychological domains and constructs, such as impulsivity, that are agnostic to the DSM nosology and have neurobiological correlates

(Kozak & Cuthbert, 2016). Barkley's theory of inhibitory deficits posits that lack of impulse control (behavioral response inhibition [BRI]) is central to ADHD (Barkley, 1997a).

Consequently, RDoC measures of BRI can serve as valid endophenotypes.

While the RDoC and Barkley's theory comprise integrated theoretical frameworks for this study, much of the endophenotype research has failed because those very measures often fail to sufficiently discriminate, segregate and dimensionalize the facets of BRI, deficits of which result in lack of impulse control. This is the problem in the literature that this quantitative quasi-experimental ex post facto study sought to address. The purpose of this study was to discriminate neurobiological and neuropsychological measures of impulsivity and BRI by assessing the relationships between subscales of the Barratt Impulsiveness Scale (BIS-11) for low and high trait motor impulsivity and subscales of three laboratory behavioral measures of BRI, the go/no-go task (GNG), stop signal task (SST), and Wisconsin card sorting test (WCST).

This study originally sought to obtain a purposive non-probability convenience sample of a minimum of 280 (as determined by G*Power version 3.1.9.7 [March 2020]) male participants aged 18-34 recruited through Qualtrics. Due to a slow uptake of participant enrollment during data collection, the sample was changed to male or female participants aged 18-40. One-way (one-factor) between subjects unpaired multivariate analysis of variance (MANOVA) was used to assess the differences among composite means of linear variates of a set of three psychometric measures (instruments) comprising dependent outcome variables from each instrument for each level for each study with post-hoc independent sample t-tests (or Welch's test) conducted when results were statistically significant to identify the source of the differences and thus, to identify novel decomposed endophenotypes (i.e., deep endophenotypes; Schumacker & Lomax, 2010).

Quadratic regression was used to discover a novel reaction time threshold to minimize commission errors for the GNG task. Cooks leverage-residual (influence) sensitivity analysis was used to improve statistical power and cross-model convergent analysis was used to identify frameworks of decomposed endophenotypes that provide optimal power-parsimony characteristics for AI feature engineering. For the purpose of this study, this process was referred to as RDoC latent variable endophenotype decomposition. Decomposed endophenotypes (deep endophenotypes) from this study can then be used as preprocessed mathematically and empirically selected features for neurocomputational models, deep phenotypes, and digital twins (see Chapter 5) of the four behavioral phenotypes described in Chapter 2 to, among other things, identify neurocomputational endophenotypes (neurophenotypes) via deep endophenotyping.

Chapter 2: Literature Review

The problem addressed by this quantitative ex-post facto quasi-experimental study is that the endophenotype literature fails to adequately characterize and segregate the dimensionality of the latent psychological constructs of impulsivity and impulse control (i.e., behavioral response inhibition [BRI]). As an explicit response to the problem, the purpose of this study was to discriminate, segregate, and dimensionalize neurobiological and neuropsychological measures (endophenotypes) through assessing the relationships between subscales of the Barratt Impulsiveness Scale (BIS-11) for low and high trait motor impulsivity (the independent dichotomous predictor variable) and lower order subscales of each of three laboratory behavioral measures of BRI: the go/no-go task (GNG), stop signal task (SST), and Wisconsin card sorting test (WCST; the dependent outcome variables).

The literature review below first provides an overview and integration of two theoretical frameworks that framed this study, the endophenotype hypothesis informed Research Domain Criteria (RDoC) of the National Institutes of Mental Health and Barkley's theory of inhibitory deficits. The discussion includes the RDoC neural systems-based approach, which implicates non-linear dynamical systems theory (NDST) and studies that use instruments that measure neural network system dynamics. Next, the literature in behavioral and psychiatric genetics is discussed to frame the endophenotype literature and the types of studies used to determine and quantify genetic liability. Following that, the literature's perspective on endophenotypes is discussed in detail.

Next, the impulsivity literature, including the literature on behavioral response inhibition (BRI), and their dimensions is discussed. Following that is a review of the literature on four DSM behavioral phenotypes that are highly heritable and polygenic and where impulsive

behavior or lack of impulse control (behavioral response inhibition) is central to their symptomatic criteria. First, two prevalent and complex primarily developmental disorders ADHD and ASD (autism) where lack of impulse control (BRI) are core manifestations of the disorders, and next, two severe complex behavioral phenotypes, borderline personality disorder (BPD) and schizophrenia, where lack of impulse control (BRI) arguably presents the most significant treatment challenges. Discussion of these DSM behavioral phenotypes includes the literature on diagnosis and treatment of these DSM disorders to help frame applications of this study discussed later.

Following discussion of the above is a review of the literature on neuropsychological, neurophysiological, and neurobiological endophenotypes. The discussion concentrates on the above DSM behavioral phenotypes. This is done in the context of the types of studies that this study can inform, including deep phenotyping. The focus is on the historical development of endophenotype studies focused on BRI, the laboratory behavioral measures used in this study and related measures, and their differences and ability to differentiate dimensions of impulsivity.

The discussion progresses in increasing complexity in study designs, towards RDoC scale agnostic deep phenotypes, ending in a greater focus on the literature using neurobiological and neurophysiological measures that focus on neural network system dynamics versus loci focused studies. Finally, a brief review of the literature of certain types of neurocomputational studies (including studies that invoke artificial intelligence, machine learning, deep learning, and digital twins) that can be informed by this study are discussed, particularly in the context of non-linear dynamical systems theory (NDST) as applied to RDoC enabled neural network dynamics.

Particular focus is paid to theory driven mechanistic neurocomputational studies and atheoretical data driven neurocomputational studies, including clustering studies that seek to

identify hidden homogenous clusters—including as unique deep phenotypes— of DSM behavioral phenotypes to better inform both differential diagnosis and treatment. This final review helps frame a key application of the findings of this study and application for future research, using a reductionist approach to dimensionalize and decompose neurobiological and neuropsychological endophenotypes to build better preprocessed mathematically and empirically selected features for holistic emergent systems based on NDST and computational neuroscience and computational psychiatry enabled neurocomputational dynamical models of impulsivity, deficits in impulse control (BRI), and behavioral phenotypes in a transdiagnostic deep phenotyping regime.

The below literature review was assembled using Roadrunner and NavigatorSearch general search tools for initial searches and EBSCOhost, ProQuest, APA Psychinfo, Google Scholar, and PubMed Central for more specific searches. Searches used either broad year ranges to capture seminal works and current year- last year- last three- and last five-year searches to capture current peer reviewed literature, dissertations, and books. Searches also included public government and organizational databases including the National Institutes of Mental Health (NIMH), certain professional organizations and on-line interviews, presentations, and academic lectures on YouTube from key knowledge leaders and experts in the domains described below to inform database searches.

Search strings included single or combinations of the following: *impulsivity, functional impulsivity, trait impulsivity, state impulsivity, choice impulsivity, impulsive action, impulsive choice, motor impulsivity, attentional impulsivity, delay-discounting impulsivity, cognitive impulsivity, inhibition, response inhibition, prepotent response inhibition, prepotent extinction, prepotent response extinction, inhibition-impulsivity binomial, impulse control, disinhibition,*

Dickman Impulsivity Inventory, self-control, self-regulation, compulsivity, ADHD, autism, borderline personality disorder, schizophrenia, affective disorders, mood disorders, bipolar disorder, paranoid personality disorder, schizoid personality disorder, schizoaffective personality disorder, antisocial personality disorder, narcissistic personality disorder, histrionic personality disorder, avoidant personality disorder, dependent personality disorder, obsessive compulsive personality disorder, Parkinsons disease; Huntington's disease, impulse control disorder, deep phenotype(s), endophenotype, endophenotype hypothesis, research domain criteria, RDoC, fMRI, qEEG, LORETA, ERP, event related potential, PET, positron emission topography, MEG, SPECT, DTI, diffusion tensor imaging, NIRS, P300, N200, neuropsychological, neurobiological, neurophysiological, impulsivity measures, self-report measures, behavioral measures, UPPS, IVE-7, Eysenck's impulsive, NEO-PI-R, BIS/BAS, SSS-V, sensation seeking, EASI, ICBC, Stroop, antisaccade, Iowa Gambling Task, Conners Continuous Performance Test, CPT, delay discounting, cognitive control, go/no-go, stop-signal, Wisconsin card sorting, WCST, BIS-11, Barratt Impulsiveness scale, Barkley's theory, DRD4-7R, neurocomputational, dynamical systems, non-linear dynamics, genome wide association studies, GWAS, candidate gene studies, case-control studies, twin studies, adoption studies, family studies, heritability of response inhibition, quantitative heritability, molecular heritability, narrow-sense heritability, broad sense heritability, heritability, polygenic risk score, quantitative trait loci, copy number variants, SNP genotyping, default mode network, neurocomputational, computational, computational neuroscience, computational psychiatry, AI, machine learning, deep learning, clustering, feature selection, feature extraction, feature engineering, predictive, autoencoders, hidden Markov models, Dirichlet mixtures, overparametized autoencoders, autoencoders, explainable AI, Causal AI.*

Theoretical and Conceptual Frameworks

This study integrated two conceptual and theoretical frameworks, the Research Domain Criteria (RDoC) developed by the National Institutes of Mental Health (NIMH) and Barkley's theory of inhibitory deficits (Barkley, 1997a; Barkley, 1999). The RDoC is largely founded on the endophenotype hypothesis and has a behavioral neuroscience perspective. Barkley's theory of inhibitory deficits was used to frame impulsivity and behavioral response inhibition (BRI) and their facets as putative RDoC endophenotypes. Each is discussed below. Following that is a discussion of other theories considered, including dynamic causal modeling and non-linear dynamical systems theory (NDST), which is discussed in the context of assumptions made and implications and recommendations for future studies. Finally, is a discussion of integration of these theories and challenges to integration.

The Endophenotype Hypothesis and the Research Domain Criteria (RDoC)

Just over fifty years ago at the time of this writing, Gottesman and Shields (1973) introduced the term endophenotype to the behavioral neuroscience related field of psychiatric genetics. They adapted the term endophenotype from John and Lewis (1966), who had contrasted it with exophenotypes, in that endophenotypes described phenotypes that were internal, non-obvious, microscopic, and measurable via microscopic observation or biochemical assay. In the five decades since its introduction, the term endophenotype evolved to describe latent non-obvious and non-apparent or otherwise hidden variables that comprise mediational phenotypes that can, nonetheless, be quantitatively measured by proxy and used in the etiological inquiry of the path from genotype to behavioral phenotype (Gottesman & Gould, 2003). While the term endophenotype is often used interchangeably in the literature with the terms intermediate phenotype and biomarker, as discussed later in this chapter, these terms are not

interchangeable and the current iteration of endophenotype differentiates it from the other two terms through, at a minimum, its genetic liability (Donati et al., 2020; Lenzenweger, 2013; Sanchez-Roige & Palmer, 2020).

The so called endophenotype hypothesis posits that endophenotypes are more homogenous and tightly linked with respect to their genotype because they are phylogenetically more proximate to genotype than their manifest behavioral phenotype, thus putatively facilitating easier study and diagnostic inquiry of derivative psychopathological disorders (behavioral phenotypes), or generally with respect to the study of personality liability (DiLalla et al., 2017; Donati et al., 2020; Sanchez-Roige & Palmer, 2020). Consequently, trait and state specific endophenotypes (e.g., trait motor impulsivity and its state facet, behavioral response inhibition) are often more appropriate biological and behavioral targets for the study of genetic linkages for such psychopathological disorders or personality traits and their neuropharmacological interventions (Crosbie et al., 2008; DiLalla et al., 2017; Eisenberg et al., 2007; Ging-Jehli et al., 2021; Iacono, 2014; Jonas & Markon, 2014; Meyer-Lindenberg & Weinberger, 2006; Tye et al., 2011).

Endophenotypes are a focus of research because they are thought to enable more directed study of genetic etiologies for so called polygenic heterogeneous and multifactorial psychiatric disorders, personality traits, and other behavioral phenotypes that share a phylogenetically upstream endophenotype, such as behavioral response inhibition deficiency and its related neurobiological and neuropsychological measurable embodiments (Crosbie et al., 2008; Eisenberg et al., 2007; Ging-Jehli et al., 2021; Jonas & Markon, 2014; Meyer-Lindenberg & Weinberger, 2006; Sanchez-Roige & Palmer, 2020; Tye et al, 2011). Thus, the endophenotype hypothesis presupposes that endophenotypes can be used to more precisely and simply identify

susceptibility genes (alleles that can become the focus of so called candidate gene studies) and to facilitate determination of the functional consequences of given allelic genotypes— that is, the biological etiology of a cognate behavioral phenotype, which can inform not only personality psychology, but also abnormal psychology and a DSM diagnostic regime and nosology that is phenomenological and not etiological (Chen et al., 2012; DiLalla et al., 2017; Reif et al., 2023; Ritsner & Gottesman, 2009; Robbins et al., 2012; Sanchez-Roige & Palmer, 2020; Walters & Owen, 2007). The endophenotype hypothesis' assumptions of genetic liability and its transdiagnostic perspective have made it an ideal foundation for the NIMH's Research Domain Criteria (RDoC; Anderzhanova et al., 2017; Forstner, et al., 2023; Iacono, 2016; Kozak & Cuthbert, 2016; Miller & Rockstroh, 2013; Reif et al., 2023).

One exemplary reason why endophenotype research has become more common in general and quantitative psychology through behavioral neuroscience is the emergence of the Research Domain Criteria (RDoC) promulgated by the National Institutes of Mental Health (NIMH; Cuthbert, 2015; Forstner et al., 2023; Gagnon et al., 2022; Insel et al., 2010; Kozak & Cuthbert, 2016; Reif et al., 2023; Sanislow et al., 2022). The RDoC attempts to provide an alternative categorical framework to the DSM and ICD nosology (and related constructs for behavioral traits; Forstner et al., 2023; Gagnon et al., 2022; Kozak & Cuthbert, 2016; Reif et al., 2023). Both the DSM and ICD define psychopathology (and traits) based on symptomatic deviations from normalized behavior.

The more recent Hierarchical Taxonomy of Psychopathology (HiTOP) does dimensionalize symptom clusters from the bottom up as covariates of mental disorders, arguably representing an important advance over the DSM and ICD, but is still somewhat mapped onto the ICD-11 nosology (Kotov et al., 2022; Kotov et al., 2021; Kotov et al., 2017; Rief et al.,

2023). In contrast, the RDoC creates observable behavioral domains, constructs, and sub-constructs for psychopathological states, each firmly grounded in neurobiological and neuropsychological etiology and measures (units of analysis) and founded in behavioral neuroscience (Forstner et al., 2023; Gagnon et al., 2022; Kozak & Cuthbert, 2016; NIMH, 2023; Sanislow et al., 2022).

The RDoC addresses a disconnect between emerging research findings from molecular and psychiatric genetics studies and neuroscience studies that use neuroimaging, for example, and DSM categorical mental disorders (behavioral phenotypes; Anderzhanova et al., 2017; Forstner et al., 2023; Gagnon et al., 2022; Kozak & Cuthbert, 2016). Thus, the RDoC attempts to reconcile an apparently false premise in the literature, that categorical DSM mental disorders (behavioral phenotypes) are unitary constructs with unique pathophysiology and psychopathology that can be tied to specific unique neurobiological etiology (Kozak & Cuthbert, 2016; Rief et al., 2023). The failure of psychiatric and behavioral genetics and neuroscience research to map onto the DSM nosology points to the square peg and round hole challenge of merging two different conceptual frameworks, the transdiagnostic nature of molecular genetics and neuroscience and diagnostic categories of the DSM.

The RDoC, therefore, subscribes to the endophenotype hypothesis. That is, lower order mediators, such as cognition and impulsivity (which can be both symptoms or endophenotypes), of downstream DSM behavioral phenotypes (mental disorders), may better map onto neurobiological correlates than onto the more complex DSM behavioral phenotypes, which are syndromal aggregates of symptoms (Gagnon et al., 2022; Kozak & Cuthbert, 2016; Rief et al., 2023). That is to say, underlying the RDoC is the previously described premise that

endophenotypes are better targets for research to understand the connection between neurobiological correlates and behavioral phenotypes (Gagnon et al., 2022).

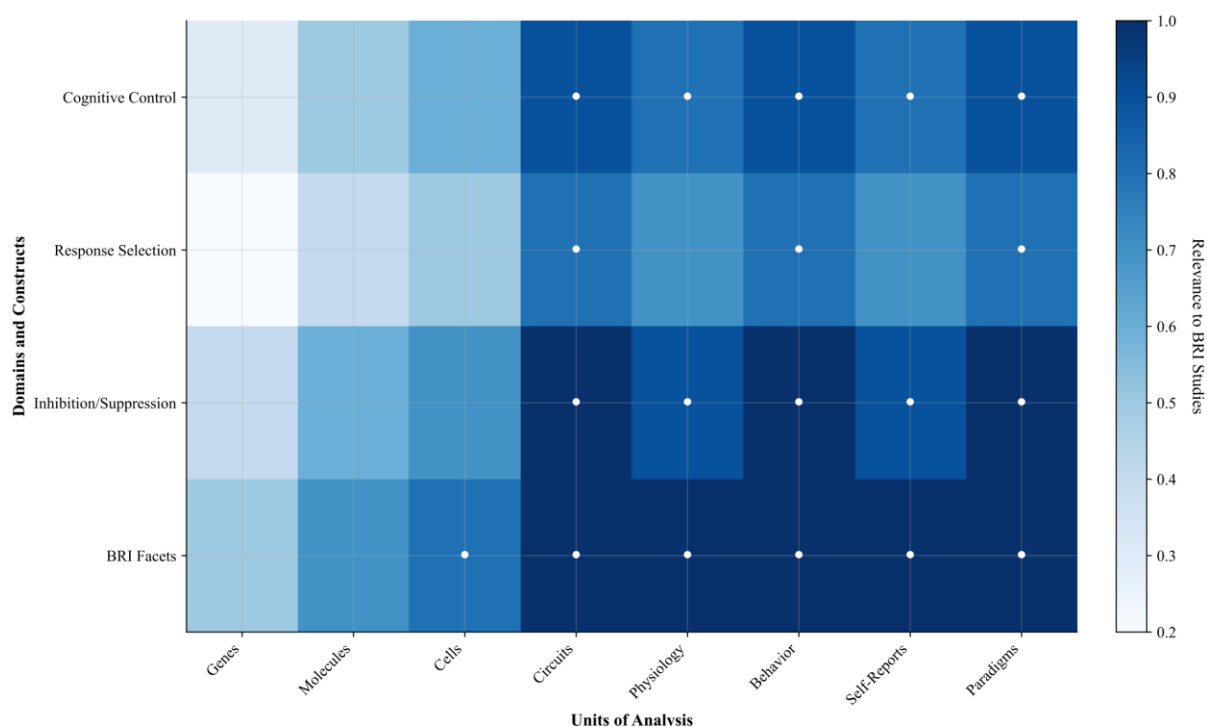
The RDoC is a framework from which to design and conduct research that is based on a matrix of neurobiological and neuropsychological measures (units of analysis and measures comprising dependent variables) and behavior that can be observed (domains, constructs, and subconstructs comprising independent variables; Forstner et al., 2023; Gagnon et al., 2022; Kozak & Cuthbert, 2016; Sanislow et al., 2022). The RDoC first takes a dynamical systems based approach (see NDST discussion below) implicating neural networks or circuits (often called network analysis) for specific behaviors, indifferent (agnostic) to DSM nosology, and then assumes a behavioral neuroscience theoretical foundation that uses psychometric and behavioral instruments (neuropsychological operational endophenotypes) and neurophysiological instruments (neurobiological operational endophenotypes) to measure (operationalize) behavioral endophenotypes (arguably characterized as a latent variable model approach), such as cognition, executive functions (EF), impulsivity, and BRI (Gagnon et al., 2022; Kozak & Cuthbert, 2016; Rief et al, 2023).

The RDoC matrix comprises, on one axis, domains and constructs (and sub-constructs) of observable behavior (independent variables), currently six domains, 25 constructs, and 26 sub-constructs, and, on the other axis, eight units of analysis (level of operational measures [dependent variables]; Forstner et al., 2023; Hepp et al, 2023; Kozak & Cuthbert, 2016; NIMH, n.d.; Sanislow et al., 2022). So, for example, BRI might fit under the RDoC domain of “Cognitive Systems” and construct of “cognitive (effortful) control” and sub-construct of “response selection; inhibition/suppression” (Hepp et al, 2023; NIHM, n.d.), although, as described in the discussion of BRI below, not all facets of inhibition are cognitive, suggesting the

RDoC may lack fully robust domains and constructs. This made the RDoC ripe for the purpose of this study. Units of analysis (measures) include genes (measured with genotyping instruments) and behavior (measured using neuropsychological psychometric and behavioral instruments)—in this case, BRI. Among units of analysis in the RDoC matrix are also self-report measures, which include categorical symptom descriptors and instruments linked to DSM nosology (e.g., ADHD; NIMH, 2023). The paradigms units of analysis under the RDoC include specific instruments such as the go/no-go task (GNG), stop-signal task (SST) and Wisconsin card sorting test (WCST) discussed briefly in this chapter and in detail in chapter 3 (Hepp et al, 2023; Kozak & Cuthbert, 2016; NIMH, 2023). The RDoC has been applied to the study of executive functions (EF), impulsivity, BRI, and numerous DSM mental disorders. Figure 1 shows an RDoC matrix adaptation specific for BRI studies.

Figure 1

RDoC Matrix Structure for Behavioral Response Inhibition Studies



A fundamental requirement for an RDoC study is that the study design cannot rely on DSM case control diagnostic labels and participant groupings but must be transdiagnostic across units of measure (including neuropsychological and neurobiological measures) and focus on psychological constructs and subconstructs, such as impulsivity and BRI, rather than DSM categorical mental disorders (behavioral phenotypes; Forstner et al., 2024; Gagnon et al., 2022; Hepp et al., 2023; Rief et al., 2023). However, that is not to suggest that RDoC studies cannot focus on, reference, or directly implicate and inform DSM disorders, including their etiology and diagnosis. The RDoC explicitly includes applications to DSM nosology, from, for example, prodromal subclinical pathology, association between endophenotypes and behavioral phenotypes (mental disorders), informing subtyping of DSM nosology, imparting risk of development of a DSM endpoint diagnosis, and identifying dimensional aspects of DSM nosology (Forstner et al., 2024; Sanislow et al., 2022). Similarly, RDoC can inform and be complementary to HiTOP (Rief et al., Kotov et al., 2021). Further the RDoC invites studies that help develop and refine existing RDoC domains, constructs, and subconstructs, including creating new constructs or subconstructs or associations between novel or refined units of analysis (measures) and existing constructs and subconstructs (NIMH, 2023; Sanislow et al., 2022). Like with the HiTOP, the RDoC is intended to be more dynamically fluid than either the DSM or ICD (Rief et al., 2023). This study is one such study that informs both of the above RDoC aims. Importantly, the RDoC, via its transdiagnostic scale agnostic units of analysis, domains, and constructs provides a template for developing unique precision and personalized deep phenotypes of behavioral phenotypes, including through the use of deep endophenotyping (Krčmář et al., 2023).

Exemplary RDoC Studies. The RDoC first assumes that transdiagnostic endophenotypes that are contained in DSM categorical mental disorders can be studied independent of DSM behavioral phenotypes (Gagnon et al., 2022). Such endophenotypes can then be studied in the context of a DSM behavioral phenotype to inform differential diagnosis, for example (Gagnon et al., 2022). Gagnon et al. (2022) invoked the RDoC framework to study ADHD using diffusion tensor imaging (DTI) in conjunction with neuropsychological measures to identify neural network circuit endophenotypes that can facilitate differential diagnosis. Bong et al. (2020) applied the RDoC framework to the construct of executive function (EF) as an endophenotype of anxiety using psychometric instruments to measure EF and quantitative electroencephalography (qEEG) using event related potentials (ERPs; described in detail later in this chapter) to measure neural correlates representing neural networks (network analysis). Bong et al. (2020) confirmed previous research that identified an ERP component known as P3 (P300), which can serve as a candidate neurobiological endophenotype for EF (the latent variable) of its own. Demetriou et al. (2019) applied the RDoC framework to EF as an endophenotype of autism spectrum disorder (ASD) to study its neurobiological underpinnings. The authors included models of EF linked with behavioral regulation, including response inhibition, and prefrontal cortical correlates (Demetriou et al., 2019). Measures (RDoC units of analysis) of BRI included the stop-signal task (SST) and go/no-go (GNG) task, and prefrontal cortical correlates included the Wisconsin card sorting test (WCST, Demetriou et al., 2019). Each is described below in discussions of neuropsychological endophenotypes following discussions of impulsivity, BRI, and the selected implicated behavioral phenotypes.

Barkley's Theory of Inhibitory Deficits

Nearly three decades ago, as of this writing, Barkley proposed a theory for attention deficit hyperactivity disorder (ADHD) in an effort to unify existing hypothesis as well as historical characterizations that were atheoretical in nature (Barkley, 1997a). His so-called theory of inhibitory deficits was strongly influenced by the field of behavioral neuroscience and theories related to neurobiological and neuropsychological underpinnings of human behavior. It posits that deficits in behavioral response inhibition (BRI), which implicate impairments in neurobiological prefrontal cortical functional systems including prefrontal, right inferior prefrontal, dorsolateral prefrontal, orbitofrontal, and striatal ventromedial neuroanatomical regions and their associated dopaminergic neural network systems, are seminal to ADHD (Barkley, 1997a; Crosbie et al., 2008; Özkan & Haznedaroğlu, 2023; Wu et al., 2023). In other words, while, historically, key deficits of inattention and hyperactivity were thought to be the hallmarks of ADHD, Barkley (1997a) suggested that deficits in BRI marked the central deficiency of ADHD. Further, while Barkley agreed that ADHD is substantially a so-called executive function deficiency disorder, and BRI is generally considered a key executive function (Filipovska & Ajdinski, 2023; Nash et al., 2013; Özkan & Haznedaroğlu, 2023; Wu et al., 2023), Barkley (1997a) posited that BRI is not an executive function per se. Instead, he posited that proper functioning of BRI is a condition precedent to proper functioning of four higher order neuropsychological cortical executive functions. These are the executive functions comprising self-regulatory processes that weigh the benefits of immediate versus delayed consequences of a given response, working memory, internalization of speech, and reconstitution, which is the novel creation of goal directed responses (Filipovska & Ajdinski, 2023; Harrier & DeOrnellas, 2005; Özkan & Haznedaroğlu, 2023). Barkley (1997a) posited that the inhibitory process creates

the delay (a cognitive moment) necessary for these executive functions to be properly engaged. In other words, deficiencies in the behavioral inhibition system (BIS) essentially undermine proper function of key prefrontal cortical executive functions that are compromised in psychopathologies, such as ADHD. Consequently, since ADHD is considered a heterogeneous polygenic disorder (behavioral phenotype) that is as much as 80%-90% heritable and thus has a very strong genetic etiology, in light of the endophenotype hypothesis, BRI is a seminal endophenotype for ADHD and ripe for rigorous study (Crosbie et al., 2008; Larsson et al., 2014).

To more precisely categorize his precedent construct, Barkley (1997a, 1997b, 1997c) parsed three facets or categorical processes of behavioral response inhibition: (a) prepotent response inhibition (action restraint or stopping before starting), which comprises inhibition of a response that is subject to the availability of immediate positive or negative reinforcement or for which such reinforcement has been primed through conditioning, (b) inhibition (extinction) of an ongoing response (action cancellation or stopping after starting) that has already begun (discussed in this study as prepotent response extinction), and (c) maintenance of the inhibitory process (interference control).

While Barkley proposed his theory specifically for ADHD, once informed by and integrated with the endophenotype hypothesis, this study expanded its application more broadly to other behavioral phenotypes, psychopathological or personality trait focused, with the benefit of Barkley's categorical distinctions to help dimensionalize neurobiological and neuropsychological endophenotypes of BRI. While not necessarily consistent with the then extant literature, these categorical distinctions suggested distinct processes and complex systems that have unique neurobiological and neuropsychological underpinnings including separate

dynamical dopaminergic neural network systems, or at least separate system dynamics, to operationalize them.

Other Theories Considered

Numerous theoretical and conceptual frameworks were considered for this study. First, were competitive frameworks to Barkley's theory of inhibitory deficits to frame impulsivity as a psychological construct and deficits in impulse control as its operationalized psychopathology. For example, while even psychoanalytic theories were considered, such as that by Jones and Allison (2010), the behavioral neuroscience and RDoC focused perspective of this study led to numerous theories framed from that dimension, including application to neurocomputational modeling in computational neuroscience. Among these theories were the neuroenergetics theory of ADHD (Killeen et al., 2013), and the basal ganglia model, dopamine transfer deficit theory, moderate brain arousal model, and dynamic development theory (Ziegler et al., 2016). While the basal ganglia model and dopamine transfer deficit theory were strongly considered, the dynamic development theory was most strongly considered and is discussed in detail below. It was not chosen for similar reasons as the above two theories. However, future studies informed based on these theories can be informed by this study.

Second, were theories to identify a conceptual framework to frame the foundation of understanding impulsivity and impulse control in both a brain behavioral intermediate model and neural network systems perspective. Non-linear dynamical systems theory is discussed in detail following the discussion of dynamic development theory. Dynamic development theory is derivative of NDST. It represents an operational embodiment of it. NDST was not chosen individually as a conceptual framework due to, among other reasons, its implicit application to

the RDoC, and is thus subsumed by the RDoC. RDoC provide both a theoretical framework via the endophenotype hypothesis and a conceptual framework that implicates NDST generally.

Dynamic Development Theory of ADHD. Sagvolden et al. (2005) proposed a dynamic development theory of ADHD, which included both impulsivity and BRI. This theory was originally considered as the primary theoretical framework for this study as it focused on identifying the key behavioral deficit of ADHD from a dynamic (implicating NDST described below) and behavioral neuroscience framed and neural network based (implicating the RDoC) perspective. Their theory posited that interactions between an underactive mesolimbic dopamine system and deficient fronto-striatal neural circuits caused deficiencies that included improper extinction of previously reinforced behavior (similar to Barkley's second facet of BRI; Sagvolden et al., 2005). However, these authors argued that BRI is a misleading construct, and the problem is not BRI, but a failure to extinguish undesirable behavior (i.e., motor impulsivity) due to a shorter time to associate the behavior with its consequences (implicating cognitive impulsivity). This results in hyperactivity where impulsivity is a side effect termed behavioral variability, which the authors suggest is a better description than BRI. Contrary to Barkley's theory, to which the Sagvolden et al. (2005) compare theirs, these authors parse impulsivity into inefficient reinforcement (reinforcement learning is discussed later in this chapter including in discussions of neurocomputational applications), failure to extinguish a previously acquired behavior, and deficient motor control (Sagvolden et al., 2005). They further argue that disinhibition (failure of inhibition/impulse control) is due to a complex interplay between neural network systems, environmental stimuli, inhibitions, and excitations (Sagvolden et al., 2005).

While the dynamic development theory relies on an RDoC friendly focus on neurobiological correlates and neural network systems, it was not chosen for several reasons.

First, it combines both cognitive impulsivity and motor impulsivity and arguably also combines, rather than segregates, lower order facets of impulsivity (disinhibition) and the neural network circuits they implicate. This study was consistent with the notion discussed by Sagvolden et al. (2005) that neural circuits, particularly, mesolimbic and mesocortical circuits, are central to impulsivity. However, this study informs studies involving those systems (including qEEG-ERP studies discussed later in this chapter), by better segregating facets of impulsivity that implicate motor impulsivity specifically, to the exclusion of cognitive impulsivity, as it implicates distinct neural circuits as previously described and as discussed in more detail later in this chapter. Barkley's theory better aligns with that goal. Second, the dynamic development theory is more difficult to test using neuropsychological measures, as it does not specify which measures measure its categorization of facets. While Barkley's theory also does not, the literature, as will be discussed later, better suggests which measures measure Barkley's facets. Third, the premise of Barkley's theory is that inappropriate motor behavior due to deficits in BRI is the core problem of ADHD. The dynamic development theory focuses on more latent complex interrelated processes that are more difficult to dimensionalize.

This study may inform dynamic development theory via better segregating the facets of BRI and impulsivity. Finally, the dynamic development theory, as a theoretical framework, implicitly maps onto non-linear dynamical systems theory (NDST), as a conceptual framework. As discussed below, NDST is focused on dynamics of complex systems. However, while NDST is also implicit in the RDoC, it was also not chosen individually as a conceptual framework for reasons discussed below. This study informs studies that may test dynamic development theory implicating NDST by first decomposing endophenotypes from a reductionist perspective, to improve the inputs into more complex studies of system dynamics. The process of decomposing

—as well as combining highly correlated factors or components— elements of a system into their facets is common in the development of neurocomputational models of complex systems in computational neuroscience, which often invokes artificial intelligence (AI), including machine learning (ML) and deep learning (DL) using, for example, multi-layered artificial neural networks (ML-ANNs; Durstewitz et al., 2023; Gagnon et al., 2022). In other words, as discussed in the final section of this chapter, better segregating and dimensionalizing elements of a complex neural system leads to more accurate development of neurocomputational models of complex neural network and emergent neurobiological systems.

Non-Linear Dynamical Systems Theory (NDST). One theory considered as a conceptual framework, non-linear dynamical systems theory (NDST), was chosen to focus on systems behavior related to impulsivity, namely neural circuit systems —often informed by qEEG/ERP studies discussed later and complementary to the dynamic development theory— rather than activity in specific brain regions —often informed by fMRI studies discussed later. NDST is a competing theory to more common reductionist theories used for DSM categorical focused research studies and is implicit in the RDoC’s neural network systems (network dynamics) focus across units of measure (dimensions; Dezhina et al., 2023; Sun & Wu, 2015). As discussed above and in the last section of this chapter, one goal of this study was to provide reductionist dimensional decomposition preprocessed mathematically and empirically selected features (decomposed endophenotypes [deep endophenotypes]) for studies that enable deep phenotyping and develop high-dimension neurocomputational models of impulsivity and BRI for specific behavioral phenotypes (including digital twins of those behavioral phenotypes) that take an emergent and wholistic NDST perspective. Consequently, although not chosen as a conceptual framework for this study, NDST is an important framework arguably implicit in the

RDoC and is discussed in detail below. Because NDST is foreign to most psychologists and psychiatrists, and somewhat foreign to neuroscientists (it is very familiar to computational neuroscientists) and behavioral and psychiatric geneticists, its development and evolution is also discussed below. First, it is discussed with respect to its historical context as a foundation to the RDoC. Next, it is discussed as a conceptual framework for neurocomputational (computational neuroscience) studies that can be informed by the better dimensionalized and segregated endophenotypes of impulsivity and BRI from this study.

In the 1940's and 1950's, the mathematically esoteric non-linear dynamical systems theory (NDST) made an almost furtive entry into the field of psychology via the then nascent field of behavioral neuroscience (psychophysiology) when behavioral neuroscientist (physiological psychologist) pioneer R. C. Davis of Indiana University attempted to apply general dynamical systems theory to his emerging field (Abraham, 1992). NDST is a theoretical paradigm in mathematics that focuses on systems that have dynamical (subject to change) properties in that multiple variables within the system can change along a time series under different parametric phase transitions that are non-linear (i.e., they are stochastic [random] and non-deterministic) or are apparently, but not actually, non-linear (i.e., they are chaotically deterministic; Favela, 2020; Favela & Amon, 2023; Guastello & Gregson, 2011; Kuś & Wójtowicz, 2024; Liu & Li, 2024). Because most complex biological systems, such as the brain and its neural network systems, behave in a non-linear or apparently non-linear fashion, NDST is ideal for use in behavioral neuroscience (Favela & Amon, 2023; Jaeger & Monk, 2014; Liu & Li, 2024; Sun & Wu, 2015). This includes the genetic, biological, and behavioral aspects of impulsivity and BRI in ADHD and other behavioral phenotypes studied via Barkley's theory of

inhibitory deficits described above. The RDoC, in addition to the endophenotype hypothesis, focuses on neural network system dynamics (Gagnon et al., 2022) and thus implicates NDST.

One seminal element of NDST is the notion that a complex system (e.g., a dynamical deep phenotype) comprising many elements, such as a personality construct (e.g., impulsivity) or a behavioral phenotype (e.g., ADHD) or the path from genotype to phenotype, is defined by the bidirectional interactions (often non-linear or apparently non-linear) between and among those elements rather than by the elements themselves (Jaeger & Monk, 2014; Kuś & Wójtowicz, 2024). In other words, a system is not defined by the sum of its parts, but by their interactions as part of the system (de Vienne, 2022; Kuś & Wójtowicz, 2024). As a system, it contains certain emergent properties that cannot be quantified via an elemental summation of its components. At any given state in time or scale, ever flowing local (i.e., Bayesian) probability theory informs the local interaction from a plurality of recent prior outcomes (Bayesian priors) to future possible outcomes (Bayesian posteriors), including transitions between states and phases, which in turn informs overall system behavior, resulting in emergent system properties (Favela & Amon, 2023; Jaeger & Monk, 2014; Kuś & Wójtowicz, 2024; Liu & Li, 2024). This contrasts with traditional reductionist approaches that avail themselves of frequentist statistics, common in behavioral neuroscience and classical science in particular.

Put another way, NDST focuses on feed-back loops between variables and accounts for temporal transitions between states, which can transition forward as well as backward, temporally or contingently (Favela & Amon, 2023; Gelfand & Engelhart, 2012; Kuś & Wójtowicz, 2024; Liu & Li, 2024). Consequently, independent variables can become dependent variables and dependent variables can become independent variables, even if they are the same variables over a time series (Favela & Amon, 2023; Gelfand & Engelhart, 2012). Traditional

reductionist approaches using frequentist statistical methods maintain distinctions between independent and dependent variables over time and do not assume bidirectional intra-elemental feedback, and essentially ignore, or at least do not focus on, dynamical and emergent properties of the system (Favela & Amon; 2023; Gelfand & Engelhart, 2012). This begs the question of why NDST remains obscure and largely unknown in psychology, and even in behavioral neuroscience. This requires consideration of its historical roots, at least in first part, to answer, and then find application to the research problem of this study via the RDoC.

Although NDST as a mathematical field arguably began in the 17th century and first found application in the highly quantitative field of physics some three-hundred years later, its vast mathematical complexity and massive computational volume required the advent of computers to provide a means for NDST to be more broadly applied to fields of chemistry, meteorology, engineering, economics, and ecology, and, eventually, biology, neuroscience and psychology proper by the mid 1970's (Aubin & Dalmedico, 2002). To the trained or intuitive eye, this order of progression proceeds from fields comprising highly quantifiable relatively simpler and more linear systems (e.g., physics) to fields with far more difficult to quantify complex and non-linear systems (e.g., neuroscience) in concert with the availability of ever-increasing computing power to quantify them.

Similarly, the path of NDST to biology, neuroscience (computational neuroscience), and then psychology (computational psychology and computational psychiatry) is a far from coincidental order of progression. It is reminiscent of the progression in the field of behavioral neuroscience, which focuses on biological predicates to behavior. NDST finds its application to behavioral neuroscience via its application in systems biology, which marks the application of NDST to biology, and includes neuronal modeling and simulation, neurogenesis, brain wave

dynamics, cortical networks, psychopathology, gene expression, brain mapping, and genotype to phenotype maps and path analysis, and the identification of endophenotypes, which are discussed above (Barrat, et al., 2013; Jaeger & Monk, 2014; Tretter et al., 2010).

Thus, the application of NDST through systems biology to neuroscience formed a key bridge to the application of NDST to psychology through behavioral neuroscience (biological psychology). In the 1970's, NDST entered psychology proper as it evolved from the transition of applications to biology, neuroscience, and behavioral neuroscience from its initial applications at the nexus of biology and psychology (Durstewitz et al., 2023; Favela, 2020). A few years later it moved into cognitive neuroscience, drawing from then recent applications in neuroscience (Favela, 2020; Guastello et al., 2009) and social systems analysis, and organizational behavior (Guastello, 2009a; Guastello, 2009b). Further, renowned developmental psychologist Esther L. Thelen, also of Indiana University, like R. C. Lewis before her, became a pioneer in the application of NDST to developmental psychology, including applications to areas related to executive functions and BRI discussed above, including cognitive development, motor development, and application to Piaget's A-not-B error, which implicates BRI via the existence of perseverative errors (PE) discussed in this study (Thelen, 2005; Thelen & Smith, 1992; Thelen & Smith, 1994; Thelen & Ulrich, 1991). Finally, NDST found practical application in clinical psychology and psychopathology in the 1980's and 1990's with clinical, essentially dynamical, disorders that exhibited cyclic or catastrophic state and phase transition behavior, including schizophrenia, bipolar disorder, unipolar depression, and dissociative identity disorder, and applying quantitative methods of structural equation modeling (SEM) and Bayesian statistics to facilitate study of their deterministically chaotic phase states and transitions (Guastello, 2009a; Guastello et al., 2009; Masterpasqua & Perna, 1997).

Despite these developments, NDST remains obscure and relatively isolated in its application to behavioral neuroscience and psychology —this informs, in part, via NDST, the bridge between computational and behavioral neuroscience. However, there are both practical applications of NDST and general conceptual benefits of its so-called systems thinking approach that can benefit traditionally reductionist fields. Reductionism can be considered not anathema to systems thinking, but an enabler of more precise study of dynamical systems generally, including with respect to the RDoC and Barkley’s theory of inhibitory deficits. This is an important premise of this study that is explored further in the last section of this chapter on neurocomputational applications. As suggested above, better inputs result in better outputs and neurocomputational models of complex neurobiological systems require more precise segregation and dimensionalization of system elements so as to better understand their interactions. Consequently, NDST was not selected for this study because it is best applied directly in the context of neurocomputational studies that employ or study emergent complex neurobiological systems (the application of computational neuroscience to behavioral neuroscience), such as dynamic development theory enabled studies, and not reductionist elemental studies, such as this study (Durstewitz et al., 2023; Liu & Li, 2024). It was also not chosen individually because it is arguably already integrated into the RDoC conceptually.

Integration and Synthesis of RDoC and Barkley’s Theory

As discussed above, the RDoC is founded on the endophenotype hypothesis and framed by NDST. Further, all these theories and frameworks find application in behavioral neuroscience, the interdisciplinary biology enabled specialization that, like cognitive neuroscience, sits within both, and at the nexus of, neuroscience and psychology. While the endophenotype hypothesis is argued to complement Barkley’s theory of inhibitory deficits,

integration of these theories with NDST in the context of the present study, is, not surprisingly, somewhat non-linear, focusing on neurocomputational applications of it (see e.g., Durstewitz et al., 2023), although all fit within the framework of the behavioral neuroscience based RDoC. Consequently, NDST is assumed in the background of the RDoC and the endophenotype hypothesis in the foreground of it.

Another goal of this study was to inform studies of facets of trait motor impulsivity and BRI that seek to quantify neurobiological and neuropsychological correlates in the context of genetic liability so as to operationalize more precise measurement of endophenotypes. Put differently, a key goal of this study was to identify narrower endophenotypes (deep endophenotypes), represented by neurobiological and neuropsychological correlates, related to facets or subsets or more primitive endophenotypes of broader constructs, such as trait motor impulsivity and BRI. The above studies typically involve neuroimaging and neurophysiological methods to study the neurobiological correlates of event driven, task dependent, exercises. For example, such studies often employ neuropsychological laboratory psychometric and behavioral measurement instruments, and they often focus on endophenotypes, such as BRI, and employ NDST's practical and conceptual solutions via the RDoC.

Neuroimaging and neurophysiological methods include functional magnetic resonance imaging (fMRI) used to study functional neuroanatomical loci (brain regions) and quantitative electroencephalography (qEEG) employing event related potentials (ERP) used to study functional neural network system dynamics (implicit in the RDoC) and, less precisely than fMRI, brain regions. Both fMRI and qEEG/ERP studies often employ NDST based data analytics, including biophysical network models and generative models, such as dynamic causal modeling (DCM; Dezhina et al., 2023; Duck et al., 2023; Frassle et al., 2021, Friston et al., 2017;

Hupen et al., 2023; Ma et al., 2015; Marreiros et al., 2010; Stephan et al., 2015). Both fMRI and qEEG/ERP also benefit from application of NDST derived advanced Bayesian statistical methods, with or without DCM, and are designed to study dynamical neurobiological and neuropsychological systems (Dezhina et al., 2023; Favela & Amon, 2023; Friston et al., 2017; Marreiros et al., 2010). fMRI and qEEG/ERP are also both used in studies (including deep phenotyping studies) in association with, and derivative of, neuropsychological (behavioral) laboratory measurements, such as the go/no-go and stop-signal tasks, which are often used for impulsivity and BRI studies. These two instruments arguably measure the first two facets of Barkley's theory of inhibitory deficits, and the Wisconsin card sorting test (WCST), which measures broader executive functions, as well as BRI.

As discussed later, unique fMRI and EEG-ERP signatures and data structures can serve as measurable endophenotypes related to the more latent BRI endophenotype. This is particularly, and most notably, common when studies using the above neuroimaging, neurophysiological, and neuropsychological methods are part of candidate gene studies (discussed later) that include allelic genotypes. More recently, such methods are used in concert with genome wide association studies (GWAS, also discussed later), because candidate genes are often of small effect sizes with respect to cognate behavioral phenotypes (Sanchez-Roige, 2020). Candidate genes for endophenotypes, however, may stand out more (via larger effect sizes) than for polygenic multifactorial psychopathological disorders, which are often characterized by a plurality of risk alleles of small effect (creating genotype maps ripe for deep phenotype study using NDST and data driven AI enabled neurocomputational studies discussed at the end of this chapter). Thus, this study may help revive the use of candidate gene studies or at least inform their use in the context of GWAS studies. Such candidate genes (alleles) include, for example,

the postsynaptic dopamine receptor four (D4) seven repeat 48 base pair variable number tandem repeat (DRD4-7R VNTR) polymorphic allele, putatively considered to link to behavioral phenotypes characterized by trait motor impulsivity, including ADHD, and deficits in BRI (Crosbie et al., 2008; Friston et al., 2017; Jaeger & Monk, 2014; Mulligan et al., 2014).

By way of example, Mulligan et al. (2014) conducted a candidate gene study of the DRD4-7R polymorphism to study BRI using fMRI while subjects, who were dichotomously divided via an ex post facto design into pretest genotype positive and genotype negative groups, performed the go/no-go task (GNG; discussed later in this chapter). Since the neuropsychological go/no-go task is designed to test for inhibition of a prepotent response to a stimulus (Barkley's first facet of BRI), it is often considered the most appropriate psychometric measure of BRI (Mulligan et al., 2014; Torenvliet et al., 2023). Much of the literature, however, considers the stop-signal task (SST; also discussed later in this chapter) the most appropriate measure or does not differentiate the two (Crosbie et al., 2008; Isherwood et al., 2023). Further, the use of fMRI, which has high spatial resolution and enables relatively precise identification of brain regions that light up, so to speak, via the proxy of blood oxygenation level dependent (BOLD) signals, during the functional neuropsychological task, enables confirmation of those neurobiological correlates (neuroanatomical regions) implicated in BRI in the literature. These include the dorsolateral, prefrontal, inferior frontal, and orbitofrontal cortex (Crosbie et al., 2008; Isherwood et al., 2023; Mulligan et al., 2014). However, functional loci enabling fMRI studies say nothing, or say very little, about the neural network dynamical systems at play other than to suggest possible points of origin, transition, divergence, or destination or vice versa for neural network node dynamical interactions and transitions. Consequently, they arguably do not integrate NDST principals per se outside of use of practical NDST tools, such as DCM,

principals that arguably can be better integrated using EEG-ERP instead, since as described later, EEG-ERP is better suited to study neural network system dynamics, thanks to its high temporal resolution. Further, Mulligan et al. (2014) observed no significant difference in go/no-go task performance between the genotype positive and genotype negative group.

What the Mulligan et al. (2014) study and many like it, arguably, failed to do is distinguish facets of BRI posited by Barkley's theory of inhibitory deficits, and, by proxy, decompose or deconstruct endophenotypes to improve effect sizes. In other words, like similar studies, Mulligan et al. (2014) assumed a relatively broad construct of BRI and a broad test for it (including agnostic use of either the go/no-go or stop-signal tasks), without inquiring as to whether it can be further elementarily parsed from a reductionist perspective.

Barkley's theory, however, can provide a theoretical framework from which to better focus neuropsychological endophenotypes, for example, from a reductionist standpoint to better inform the relationship between genotype to endophenotype and endophenotype to behavioral phenotype and the dynamical neural network systems they encompass from an NDST conceptual perspective under the rubric of the RDoC theoretical and conceptual framework. In other words, by better characterizing what a neuropsychological instrument, such as the go/no-go task, measures, which should both refine and improve its construct validity, that measurement may become a more precise endophenotype in its own right (a discriminated component of a deep endophenotype) with either stronger genetic liability or genetic liability that is less polygenic and closer to monogenic etiology, preferably resulting in improved effect sizes, particularly for candidate gene studies.

To illustrate, within the categorical framework of Barkley's theory, the go/no-go test appears to best match up with the first element, a primed prepotent response, but not the second,

interruption of an ongoing response, or the third, maintenance of the inhibitory process. There might be other instruments better suited to study those elements, particularly the second, using the stop-signal task, for example, that can better inform candidate gene studies, such as the one conducted by Mulligan et al. (2014). Such was one goal of this study. Without a theory to combine with the endophenotype hypothesis and RDoC to decompose putative endophenotypes into more differentiated neurobiological and neuropsychological components, such endophenotypes may retain a polygenic nature too proximate to the polygenic nature of the downstream behavioral phenotype, with its consequential limitations, thus undermining both the goals and efficacy of endophenotype research and the RDoC.

Numerous studies, such as Mulligan et al. (2014), seek to identify neuropsychological and neurobiological endophenotypes precedent to behavioral phenotypes with genetic liability, a path ripened by measures of brain activity such as fMRI and EEG-ERP. While even EEG related studies most often focus on functional brain regions to identify or confirm candidate genotypes precedent to neurobiological and neuropsychological endophenotypes, some focus on inter-regional dynamic interactions represented by related neural network systems, focusing more on dysfunction in connections between regions (i.e., interactions) rather than the regions themselves, an NDST and RDoC point of view. These interactions are arguably best studied using EEG rather than fMRI, and indeed NDST principals, such as graph theory (common in AI), have been applied in such settings for endophenotype research (Smit et al., 2010).

Research Domain Criteria (RDoC) as a Vehicle for Theory Synthesis. As discussed previously, an exemplary reason why endophenotype research has become more common in general psychology through behavioral neuroscience is the emergence of the RDoC. The RDoC framework provides an effective vehicle and means to integrate and synthesize NDST as an

implicit premise of RDoC, rather than individually, and the endophenotype hypothesis and Barkley's theory of inhibitory deficits.

First, a fundamental premise of the RDoC is that its categorical constructs are underwritten by dynamical neural network systems (i.e., NDST) that can be better understood through neuropsychological and neuroimaging methods (Anderzhanova et al., 2017). It is here where the conceptual integration, rather than the practical integration, of NDST became more evident in the context of this study in that NDST mathematics proper need not be integrated for the concepts of NDST systems thinking to inform endophenotype research utilizing, for example, Barkley's theory of inhibitory deficits. Practical integration of NDST, while possible, may prove more complex and was far from trivial and beyond the scope of this study, although not beyond the scope of studies it was intended to inform, as previously discussed (see last section this chapter on neurocomputational studies). For this reason, while NDST was excluded as a conceptual and theoretical framework, it is discussed in detail above. For example, the RDoC does not explicitly consider dynamical aspects of psychopathology (behavioral phenotypes) beyond the concept of its importance and focuses on biological reductionist determinism as an enabling foundation (Anderzhanova et al., 2017).

Second, the RDoC explicitly supports the endophenotype hypothesis and assumes related studies to study psychopathology and personality are founded upon it (Anderzhanova et al., 2017). Third, the RDoC does not draw firm conditional distinctions between psychopathology and psycho-normality. It assumes a conserved, relatively stable, personality trait or construct or behavioral domain that is foundationally defined by its neurobiological correlates and exists along a spectrum or continuum of behavioral expression where psychopathology is defined by marginal statistical frequency and its neurobiological correlates and traits, constructs, or domains

can be examined as risk factors (endophenotypes) in healthy subjects (Anderzhanova et al., 2017; Gagnon et al., 2022). This immediately implicates Barkley's theory of inhibitory deficits because it focuses not on the psychopathology (i.e., ADHD) itself, but on the endophenotype (i.e., BRI) that phylogenetically precedes it, and that endophenotype is agnostic to psychopathology, both as to different psychopathological disorders characterized by it, as well as personality traits generally, without reference to psychopathology. In the context of this study and beyond, not only can Barkley's theory be integrated with the endophenotype hypothesis and RDoC (and NDST), but also, it can be expanded beyond its self-prescribed nosological limitations.

In synthesizing the above theories, several features from the above discussion emerged that help frame the topic of this study. First, endophenotypes can be, and perhaps should be, agnostic to psychopathology and thus transdiagnostic. In that sense, they are akin to pleiotropic genes, in that they influence putatively differentiated behavioral phenotypes. Trait motor impulsivity and, by antecedent association, BRI is, after all, pervasive in a plurality of psychopathologies and considered a strong candidate endophenotype (Arnatkeviciute et al, 2023; Crosbie et al., 2008; Robbins et al., 2012). Second, the endophenotype hypothesis assumes lower order polygenic determinism for a given endophenotype than its manifest behavioral phenotype. That is to say, the endophenotype should, at a minimum, have fewer susceptibility genes or risk alleles than the behavioral phenotype, and as one continues to decompose an endophenotype (as this study intended), one arguably should get closer to monogenic Mendelian etiology, or, at a minimum, fewer risk alleles with larger effect. Since multifactorial polygenic disorders (behavioral phenotypes) like ADHD have a panoply of genotypic risk alleles, each exerting a relatively small effect on the behavioral phenotype, owing to replicability and small effect size

issues in the genome wide association, gene linkage, and candidate gene literature, fewer risk alleles should each exert larger effects (Crosbie et al., 2008; Sanchez-Roige, 2020). Third, following from the second point above, a given endophenotype, such as trait motor impulsivity, may not be a unitary construct, and include lower order facets, such as BRI, and, similarly, such lower order facets may not be unitary constructs, as suggested, in this case, by Barkley's theory of inhibitory deficits. This is both a reductionist perspective as one decomposes endophenotypes and a systems thinking NDST perspective as one scales forward to the emergent neurobiological systems that engage the endophenotype and the emergent behavioral systems they manifest.

Consequently, on the one hand, consistent with the endophenotype hypothesis, the lower order endophenotype, for example, prepotent response inhibition as the first element of Barkley's categorical classification of behavioral response inhibition, should in turn be less polygenic than the broader endophenotype of BRI from a reductionist perspective. On the other hand, it should differentially implicate either a neurobiological correlate comprising a unique neural network system (unique from that associated with Barkley's other two elements), or unique system dynamics if the same neural network is implicated. More operationally speaking, it should differentially implicate a unique neurophysiological or neurobiological correlate, such as a unique EEG-ERP waveform signature, representing a unique neural network or unique network dynamics, as the case may be. Fourth, in light of the above emergent features, —that is, the phylogenetically more primitive, and thus arguably developmentally earlier, position of a given endophenotype in relation to a behavioral phenotype, its agnostic or pleiotropic like relation to behavioral phenotype, and decomposition of endophenotype complexity to inform unique system behaviors— endophenotypes should serve as early predictors or primordial diagnostic markers, in healthy pre-symptomatic or prodromal individuals, of downstream behavioral phenotypes.

Similarly, upstream genotype risk alleles predict endophenotype, with consequent larger effect sizes than effect sizes between genotype to behavioral phenotype. Both putatively provide greater certainty as to any causal relation to behavioral phenotype.

The above features emerge consequentially to integration and synthesis of the above theories, and those features illustrate the synergies and, to use NDST terminology, emergent benefits possible from integrating the RDoC's endophenotype hypothesis and Barkley's theory of inhibitory deficits. Barkley's tripartite classification suggests lower order endophenotypes that may be better candidates for study (e.g., as components of deep endophenotypes) than the broader endophenotype candidate of BRI, and in turn, the endophenotype hypothesis informing that stratification. All of this is against the backdrop of NDST enabled systems thinking while assuming that reductionism can inform it. However, these features do not or cannot fully illustrate all implications of synthesis, particularly since a synthesis of NDST proper reached beyond the scope of this study, and there are conflicts that are difficult to reconcile and inhibit that integration; hence, it was not included as a theoretical or conceptual framework of this study.

Conflicts to Integration and Synthesis. Each of the above theories has challenges individually in that they conflict with or are difficult to reconcile with other existing theories and each-other. One challenge to the endophenotype hypothesis, for example, is suggested by the 20 to over 50-year passage of time, as of 2024, since introduction of the hypothesis, depending on your starting point (Gottesman & Gould, 2003). Most endophenotype research is far more recent, and fully validated endophenotypes are virtually non-existent, identified for only a handful of psychiatric and neurodevelopmental disorders (Beauchaine & Constantino, 2017; Dick, 2018;

Flint & Munafo, 2007; Hwang et al., 2023; Miller & Rockstroh, 2013; Miranda et al., 2020; Mosconi et al., 2023; Pua et al., 2023; Zhi, 2023).

The emergence of artificial intelligence, including machine learning and deep learning, potentially promises identification of additional endophenotypes (comprising deep phenotypes or deep endophenotypes) for behavioral phenotypes, such as autism (Di Giovanni et al., 2023). One reason is that the literature has struggled to confirm the endophenotype hypothesis fully in that many endophenotypes appear no less polygenic than cognate behavioral phenotypes, meaning effect sizes have not necessarily improved as to gene linkage (Beauchaine & Constantino, 2017; Dick, 2018; Flint & Munafo, 2007; Miller & Rockstroh, 2013). While the earlier discussion suggested decomposing (deep endophenotyping) candidate endophenotypes further as a goal of this study to inform this problem, there was little evidence this could be accomplished in light of Barkley's theory.

Further, as discussed above, there are many alternatives to Barkley's theory and much heated debate not limited to ADHD research regarding the central role of BRI in ADHD or psychopathology generally, some calling it misleading and challenging Barkley's theory directly (Jones & Allison, 2010; Killeen et al., 2013; Sagvolden et al., 2005; Ziegler et al., 2016). Finally, and most evidently, and a reason why it was not included separately as a theoretical or conceptual framework outside of its foundation in the RDoC, is that NDST remains on the fringes of integration into psychology, and even behavioral neuroscience. As discussed previously, full mathematical, even practical, integration with the endophenotype hypothesis and RDoC and Barkley's theory was beyond the scope of this study, but NDST does find practical application to the studies this study informs, such as neurocomputational studies (using artificial intelligence machine learning and deep learning) discussed in the last section of this chapter.

However, many have argued, often correctly, that NDST has been applied incorrectly to psychology and behavioral neuroscience or too obscurely applied for a majority of peer reviewers, who often lack the mathematical sophistication to even begin to disentangle appropriate application from inappropriate application of NDST, to properly vet NDST (Brown, et al., 2013; Gelfand & Engelhart, 2012; Pincus et al., 2018). It is these challenges that bespeak caution to integration of NDST with the endophenotype hypothesis and Barkley's theory of inhibitory deficits, but not to the extent that conceptual integration is not well advised within the framework of the RDoC.

Alignment of the Theoretical Framework with the Problem, Purpose, and Research Questions of This Study. The integrated and synthesized theoretical framework above is appropriate for developing the problem because, as stated above, a key goal of the RDoC is to better discriminate psychological constructs and Barkley's theory suggests discriminate components of BRI that can be tested, measured, and better discriminated. The theoretical framework is appropriate for developing the purpose because the measures of this study are among the units of analysis across several levels of the RDoC and are implicated in discriminating the facets of BRI under Barkley's theory. The integrated and synthesized framework is appropriate for developing the research questions because it provides a framework to identify discriminating and decomposed endophenotypes and improving the application of Barkley's theory across behavioral phenotypes consistent with the transdiagnostic perspective of the RDoC.

Behavioral and Psychiatric Genetics

Genotypes are the assembly (complete or partial) of an individual's alleles (de Vienne, 2022; Knopik et al., 2017). Alleles are the variants or versions of particular genes that occur by

token of mutations (polymorphisms) that are primarily consequential of evolutionary adaptation and natural selection (Knopik et al., 2017). Phenotypes are the observable manifestations, products, or expressions of genotypes (i.e., morphology, traits, or characteristics) in combination with environmental epigenetic factors (de Vienne, 2022; Knopik et al., 2017). Behavioral genetics is the study of the role of genotypes (including epigenetic gene-environment interactions) on behavior, which is the phenotypic output of the brain (Knopik et al., 2017). Psychiatric genetics is a sub-field of behavioral genetics that focuses on the development of behavioral phenotypes (mental disorders or psychopathology; Ellenbroek & Youn, 2016, Nurnberger & Berrettini, 2012; Schulz & McMahon, 2018). Consequently, psychiatric genetics focuses on the heritability of mental disorders.

Heritability is the fraction of variation (differences) of phenotypes that is explained by the variation of genotypes (Mayhew & Meyre, 2017; Zaitlen & Kraft, 2013). By most accounts, the heritability (genetic etiology) of mental disorders (behavioral phenotypes) ranges from .4 to .8 (Hoehe & Morris-Rosendahl, 2018). In other words, between an average of 40% to 80% of the differences between phenotypes of mental disorders are attributable to differences in genotypes of individuals with these disorders. That is to say that heritability is a measure of the degree of variability of a behavioral phenotype around the average measure of that phenotype rather than heritability of the average measure for the phenotype itself. Some behavioral phenotypes in particular (each discussed in detail later) have been determined to be highly heritable (even more than the above ranges) in the psychiatric genetics literature. For example, autism spectrum disorder (ASD), as currently defined in the DSM-5-TR, has been reported to be as high as 90% heritable (Sandin et al., 2017). ADHD has been reported to be as high as 88% heritable (Faraone & Larsen, 2019). Schizophrenia has been reported to be as high as 80% heritable (Hilker et al.,

2018). Borderline personality disorder has been reported to be as high as 70% heritable (Ma et al., 2016; Reichborn-Kjennerud, 2010; Skoglund et al., 2021).

With such high neurobiological etiology, understanding the genetic liability of behavioral phenotypes is of critical importance to inform etiology, risk, diagnosis, prevention, and treatment. Further, due to the major role of heritability in many behavioral phenotypes, a key goal of psychiatric genetics studies is to identify and quantify specific genotypic variations and determine their liability on those behavioral phenotypes (Nurnberger & Berrettini, 2012; Zaitlen & Kraft, 2013). Such studies avail themselves of the tools of molecular genetics, quantitative genetics, population genetics, statistical genetics, functional genomics, epidemiology, evolutionary biology, and phylogenetics, among others (Knopik et al., 2017; Nurnberger & Berrettini, 2012). Consequently, well designed studies that seek to identify associations between given alleles or groups of alleles, either etiological (causal) or correlational, and behavioral phenotypes can provide critical information regarding the origin, early diagnosis, prevention, and amelioration of mental disorders. Further, the design and quality, accuracy, precision, and differentiability of measures used for such studies is of particular importance to quantify the heritability of behavioral phenotypes, a focus of this study.

The heritability of behavioral phenotypes does not tell the whole story in psychiatric genetics, however. Although the heritability of mental disorders is relatively high, the percentage of phenotypic variance that has been explained and elucidated by psychiatric genetic studies is extremely low (Fisch, 2022; Zaitlen & Kraft, 2013). This is known as the missing heritability problem and can be attributed to the methods (units of measure) used to identify and quantify genetic variants (polymorphisms or alleles), rather than the traditional methods used to determine heritability, which are distinct (Fisch, 2022). From another perspective, the difference in

heritability can be attributed to the difference between quantitative heritability and molecular heritability. Quantitative heritability is determined by twin, adoption, and family studies (discussed below) and molecular heritability is determined by GWAS and other studies (discussed below) and is often much lower (40% lower or more) than quantitative heritability (Matthews & Turkheimer, 2022). This difference is the gap of missing and unaccounted and unquantified heritability by molecular genetics studies (Matthews & Turkheimer, 2022; Sun et al., 2023). For the purpose of this study, the premise that quantitative and molecular heritability measure distinct phenomena was assumed, but it is important to note that competing theories explaining the cause of the missing heritability problem abound (Fisch, 2022; Matthews & Turkheimer, 2022).

In the next section, the types of psychiatric genetics studies used to determine quantitative (traditional) heritability are first discussed. Next are discussions of the types of psychiatric genetics studies (molecular heritability) used to identify and quantify specific genotypes most responsible for phenotypic variance among psychiatric disorders (behavioral phenotypes). It is this latter group of studies that were a primary focus of this study, although, as discussed below, this study can also inform quantitative genetics study designs using quantitative heritability methods. One possible benefit of this study is to help close the gap of missing heritability by improving the accuracy, precision, and discriminate validity of measures used in such studies, measures which are or can become candidate endophenotypes.

Quantitative Genetics Studies That Determine Heritability

Arguably, the determination of the quantitative heritability of a behavioral phenotype rests on three fundamental premises. First, variations in fewer than one percent of the human genome accounts for phenotypic differences among individuals (Libiger & Schork, 2012).

Second, the closer the familial relation between individuals, the more of these genetic variations will be similar among them (Libiger & Schork, 2012; O'Connell et al., 2022). Third, to the extent that genotype contributes to liability for a behavioral phenotype, the closer the familial relation between individuals, the more likely they will share that behavioral phenotype (Libiger & Schork, 2012; O'Connell et al., 2022). These premises form the foundation of the most common psychiatric genetics studies to determine quantitative heritability of behavioral phenotypes, namely, twin, adoption, and family studies.

One additional aspect of quantitative heritability is important to frame the discussion that follows. There are two types of quantitative heritability, narrow-sense heritability and broad-sense heritability. Narrow-sense heritability describes the extent the phenotype of an individual is determined by the genotype of their parents (Libiger & Schork, 2012; Mayhew & Meyre, 2017; O'Connell et al., 2022). Broad-sense heritability is a bit more complex. It can be defined as the sum of additive and non-additive effects of genotype, divided by the sum of phenotypic variation (Libiger & Schork, 2012; Mayhew & Meyre, 2017; O'Connell et al., 2022). Additive effects comprise the effect of a given allele at all locations (loci) that influence a given phenotype (Libiger & Schork, 2012; Mayhew & Meyre, 2017; O'Connell et al., 2022). Put differently, the production of an intermediate phenotype (or an endophenotype) by a heterozygous genotype (a genotype comprising different alleles [polymorphisms] of a given gene) when compared to homozygous genotype (a genotype comprising identical alleles) results in additive genetic variation (Libiger & Schork, 2012; Mayhew & Meyre, 2017; O'Connell et al., 2022). Non-additive effects include gene-gene interactions between alleles at the same locus (dominance) or between those at different loci (unrelated genes or epistasis; Libiger & Schork, 2012; Mayhew & Meyre, 2017; O'Connell et al., 2022). Dominance occurs when a similar

phenotype is produced by a heterozygous genotype to that produced by a homozygous genotype with identical alleles (Libiger & Schork, 2012; Mayhew & Meyre, 2017; O’Connell et al., 2022). Epistasis occurs when a dominant allele of one gene suppresses the effect of an allele of another unrelated gene and is phenotypically expressed (Libiger & Schork, 2012; Mayhew & Meyre, 2017; O’Connell et al., 2022).

It is not always clear however, whether a given heritability study is measuring narrow-sense heritability or broad-sense heritability. It turns out that the heritability literature appears to suffer from similar problems as the endophenotype, impulsivity, and BRI literature—that is, a failure to adequately segregate and dimensionalize its facets (Martens et al., 2016; Tenesa & Haley, 2013). Many heritability studies fail to distinguish the type of heritability that is being measured, making it difficult to reproduce results, compare or evaluate methods, and conduct proper meta-analysis, among other issues, particularly considering that broad-sense heritability is equal to or greater than narrow-sense heritability for a given sample of twins (Martens et al., 2016; Mayhew & Meyre, 2017; Tenesa & Haley, 2013). Consequently, this limitation must also be considered when discussing and evaluating twin, adoption, and family heritability studies below. As suggested above, somewhat similar issues to those this study can address with the endophenotype literature also occur in the psychiatric genetics literature, namely lack of discrimination among measures and differentiation regarding what is being measured (Martens et al., 2016; Tenesa & Haley, 2013).

Twin Studies. Applying the above premises, twin studies are a common method of determining heritability of behavioral phenotypes. Monozygotic (identical) twins are genetically identical (and of the same sex), have the same additive and non-additive effects on their genomes, and share the same general environmental factors, such as shared socioeconomic

status, prenatal environment, and general upbringing (Knopik et al., 2017; Mayhew & Meyre, 2017). Where they differ is in unique environmental factors, such as differences in individual upbringing and lifespan development (Knopik et al., 2017; Mayhew & Meyre, 2017). Consequently, differences in behavioral phenotype or traits can be attributed to unique environmental factors. Dizygotic (fraternal) twins share 50% of their DNA (and can be of opposite or same sex), but also have the same shared environmental factors, and similarly differ in unique environmental factors as monozygotic twins do. The extent to which a behavioral phenotype correlates (concordance rate) among and between monozygotic and same-sex dizygotic twins can assist in determining the contribution of additive and non-additive effects to phenotypic variance (Mayhew & Meyre, 2017). The classical twin method (CTM) comprises subtracting the within groups correlation of monozygotic twins from the within groups correlation of dizygotic twins multiplied by two to provide an estimate of broad sense heritability (Mayhew & Meyre, 2017). In other words, if monozygotic twins are more similar in their behavioral phenotype or a given trait, then that difference can be attributed to genotype (Ferrera & Nurnberger, 2022; Knopik et al., 2017).

Where twin studies fall short is in their assumptions. They assume that shared environmental influences are identical, which is not always the case (Hwang et al., 2021; Knopik et al., 2017; Mayhew & Meyre, 2017). They also minimize the influence of gene-environment interactions and epigenetics (Mayhew & Meyre, 2017). This may result in exaggerated heritability estimates because these differences are assigned to genotype rather than environment and its impact on gene expression, a consequence that can be compounded by results reporting broad-sense heritability rather than narrow-sense heritability, since the former is typically higher than the latter (Knopik et al., 2017; Mayhew & Meyre, 2017).

Most twin studies avail themselves of very large twin registries and databases to increase statistical power, but many do not distinguish between narrow-sense and broad-sense heritability. Larsson et al. (2014) used the Swedish Twin Register of nearly 60,000 twins to determine the heritability of ADHD. However, the authors did not indicate whether they were measuring narrow-sense heritability or broad-sense heritability. Johansson et al. (2019) used the CTM design to study 462 twins to determine the heritability of schizophrenia and bipolar disorder. But the authors did not differentiate between narrow-sense and broad-sense heritability. Skaug et al. (2022) studied 2,808 twins from the Norwegian Medical Birth Registry to study the concordance of heritability of BPD traits and childhood trauma. Unlike many studies, it was clear that the authors measured narrow-sense heritability. Finally, as an example of twin studies that seek to identify biomarkers (and endophenotypes), Fu et al. (2022) studied the heritability of abnormalities in limbic neural networks of 66 twins with autism spectrum disorder using diffusion tensor imaging (DTI; discussed later in this chapter). However, the authors did not distinguish between narrow-sense heritability and broad-sense heritability, which again, includes more factors and thus is often reported as higher. Again, with regard to the focus of this study, this is an example of failure to properly differentiate and dimensionalize facets of a construct, that can reduce the efficacy of studies that purport to measure that construct.

Adoption Studies. One way to address the questionable shared general environment assumption of twin studies is to study twins (monozygotic or dizygotic) who have been adopted and raised in different environments (Ferrera & Nurnberger, 2022; Mayhey & Meyre, 2017). Because environmental effects are distinct and segregated, any correlation between twins in a twin dyad can be assumed to be due to genotype and comprise an estimate of broad-sense heritability (Ferrera & Nurnberger, 2022; Mayhey & Meyre, 2017). Similarly, biologically

unrelated adopted children share the same general environments, but do not share genotype. In that case, any correlation between adopted, but unrelated, siblings can be attributed to environmental effects and not genotype (Ferrera & Nurnberger, 2022; Knopik et al., 2017; Nurnberger & Berrettini, 2012). These two types of adopted dyads produce genetic relatives and environmental relatives (Knopik et al., 2017; Nurnberger & Berrettini, 2012).

While adoption studies are generally considered better estimates of heritability, they also have assumptions that may be problematic. Complete segregation of environmental effects is not always certain, such as in cases where the adoption of twins occurs later in life after they shared general environmental effects (Mayhey & Meyre, 2017). Even in cases where adoption occurs shortly after birth, twins still share the same pre-natal and post-natal environmental effects (Ellenbroek, 2016). Further, the very motive or socioeconomic status of biological and adoptive parents may not, in each case, represent the entire population, since biological parents in such situations are more likely to be from low socioeconomic status and adoptive parents are more likely to be from higher socioeconomic status (Mayhey & Meyre, 2017).

Like certain twin studies, adoption studies can be used to identify biomarkers (and endophenotypes). Myllyaho et al. (2022) studied adopted twins from the Finnish Adoptive Family Study of Schizophrenia to assess the effects of socioeconomic status (an environmental effects factor), family functioning, and genetic liability and identify risk factors (which can be endophenotypes to the extent tied to genetic liability). Sellers et al. (2020) sought to quantify the effect of unique environmental effects of child rearing on ADHD twin dyads and aggression via an unrelated parent-child adoption study. These are examples where traditional study designs used for traditional quantitative heritability studies can be used in endophenotype research, and can also be informed by this study.

Family Studies. Family studies sample dyads with similar consanguinity with groupings based on specific relationships (e.g., 1st degree sibling studies and parent-child studies, 2nd degree first cousins, etc.) and focus on calculating narrow-sense heritability (Ellenbroek, 2016; Ferrera & Nurnberger, 2022; Mayhey & Meyre, 2017). Like with other types of studies, there are limitations. Family studies of siblings, for example, ignore shared environmental effects and non-additive genetic effects, as well as assume a uniform 50/50 contribution of genes from parents where inheritance deviates in the range of 37%-62% shared genotype (Mayhey & Meyre, 2017). Further, many studies of heritability utilize various combinations of twin, adoption, and family studies to increase power and expand the relationships that can be studied (Knopik et al., 2017; Nurnberger & Berrettini, 2012).

Synthesizing the above types of studies with the psychological construct that was the focus of this study, Bezdjian et al. (2011), conducted a meta-analysis of 41 key twin, adoption, and family studies covering over 27,000 individuals to quantify genetic and environmental liability on impulsivity. The authors noted that impulsivity was not a unitary but a multidimensional construct and comprised various facets, features, or factors and, as of 2011, had been the target of over 100 twin, adoption, and family studies. They further identified ADHD and borderline personality disorder among those mental disorders strongly implicated by impulsivity (Bezdjian et al., 2011). Most such studies indicated both additive and non-additive genetic effects largely explained liability for impulsivity (Bezdjian et al., 2011). The authors observed that some facets of impulsivity were significantly more heritable than others (Bezdjian et al., 2011). Further, in discussing historical studies, the authors noted a bifurcation in methodology (units of analysis to use RDoC terminology): self-report measures, including the BIS-11 used in this study, and laboratory behavioral measures (behavioral and psychometric

laboratory tasks or neuropsychological measures), including the go/no-go (GNG) and stop-signal (SST) tasks used in this study. They also noted that certain laboratory behavioral measures focus on deficits in behavioral response inhibition (disinhibition). The authors further noted that the results of behavioral and psychiatric genetics studies were influenced by the types of measures used to quantify impulsivity and its facets. One inference that can be made from the above observations is that if the wrong (or a less optimal or applicable) measure is used to quantify a facet of impulsivity (or quantifies the wrong facet), or fails to differentiate distinct facets in a twin, adoption, or family study of impulsivity, then results of such studies may be misleading or may overstate or understate the genetic liability of the construct or of its individual facets. This is another example of the problem this study can help address (Tenesa & Haley, 2013).

Molecular Genetics Studies That Determine Genetic Liability

As stated above, quantitative genetics studies of heritability (quantitative heritability) focus on the determination of the cumulative effect, at a macro-level, of the relative contributions of genetic (agnostic to individual genes) and environmental (agnostic to individual environmental influences) liability on behavioral phenotypes. Molecular genetics studies (molecular heritability) focus on the contribution of individual genes at the molecular (DNA) level (to the exclusion of environmental effects) to the genetic liability of behavioral phenotypes (Ferrera & Nurnberger, 2022; Knopik et al., 2017; Nurnberger & Berrettini, 2012; Tsermpini et al., 2022). In other words, quantitative heritability studies seek to identify the liability of all genes on a behavioral phenotype. Molecular heritability studies seek to identify the liability of individual genes (specifically, alleles) on a behavioral phenotype.

The above distinction between quantitative and molecular heritability may lead to an additional inference regarding the missing heritability problem. The missing heritability problem

may simply be explained by the failure of molecular genetic studies to date to identify all alleles that contribute to genetic liability of a behavioral phenotype that are accounted for, in the aggregate, by quantitative genetic studies (Ferrera & Nurnberger, 2022; Knopik et al., 2017). As stated above, this study operated under the premise that quantitative heritability and molecular heritability measure different phenomena. The above inference is arguably consistent with that premise. Also consistent with that premise was a focus of this study, to better discriminate and dimensionalize facets of impulsivity and BRI in that it can help identify credible alleles more easily identified by decomposing endophenotypes to close the gap of the missing heritability problem.

Molecular genetic studies that determine the heritability of behavioral phenotypes focus primarily on identifying a plurality of implicated individual alleles rather than one allele (one gene) that imparts liability on a behavioral phenotype. There are, however, certain neurological diseases, such as Huntington's disease, Fragile X syndrome, monogenic autism, and certain forms of Parkinson's disease and ALS, that are monogenic in that they are etiologically tied to a polymorphism (allele) of one gene with strong effect typically identified by linkage analysis studies (described below; Chen et al., 2020; Knopik et al., 2017; Tong et al., 2024). Monogenic diseases are rare because a single polymorphism leading to a unique phenotype is statistically rare (Chail et al., 2008; Roofeh et al., 2013). A single allele leading to a unique phenotype contrasts with a plurality of alleles leading to a complex phenotype (Chail et al., 2008; Ferrera & Nurnberger, 2022). Monogenic diseases also subscribe to Mendelian genetics principals of natural selection and are frequently naturally selected out of population level inheritance (Blekhman et al., 2008). Hence, monogenic diseases are often called Mendelian diseases (Chail et al., 2008).

Polygenic diseases and disorders are caused by a plurality of alleles, each with relatively weak effect (i.e., each predicting a small portion of phenotypic variance) and comprise a majority of DSM behavioral phenotypes that have strong quantitative genetic liability (Knopik et al., 2017; O’Connell et al., 2022). Thus, the molecular genetics studies discussed below do not focus so much on identifying a single seminal gene or allele that imparts absolute or statistically probable liability on a behavioral phenotype with large effect, but on identifying individual risk alleles that increase fractional liability for a particular behavioral phenotype from a theoretical baseline of zero (Knopik et al., 2017; Tenesa & Haley, 2013). According to one theory of risk allele liability, at some point, if an individual has a sufficient number of unique risk alleles for a given disorder, they reach what is called the liability-threshold and are affected with that disorder (Knopik et al., 2017). Other theories, however, posit that a continuum of polygenic risk and disorder manifestation is primarily a product of symptom severity or epigenetic effects on risk alleles (Knopik et al., 2017).

Although identifying individual risk alleles as groups for polygenic disorders is the current focus of molecular genetics studies, identifying individual alleles (polygenic predictors), even those of relatively small effect, can provide biological targets for potential psychopharmacological or other biologic interventions to treat mental disorders that quantitative genetics studies that determine quantitative heritability do not provide (Gorlov et al., 2011; Knopik et al., 2017). Identifying such individual risk alleles that have relatively large effect compared to other risk alleles for a given behavioral phenotype should provide more optimal targets for such interventions (Gorlov et al., 2011; O’Connell et al., 2022). This is a key premise this study informs. As discussed later in this chapter, endophenotypes are closer to their genetic origins, so individual risk alleles that impart liability on those endophenotypes should have larger

effect sizes than they do with respect to their downstream behavioral phenotypes. This study addressed a key aspect of identifying such risk alleles, that is, improving or discriminating the coupling of the dyad between units of measure (under RDoC) and the individual endophenotypes they are used to quantify. This is accomplished through a process of decomposing those endophenotypes to more fundamental component endophenotypes. Those component endophenotypes would putatively have stronger links to their risk alleles with larger effects sizes against those decomposed endophenotypes than against a broader less discriminated or less dimensionalized endophenotype. Candidate gene studies, in particular, seek to identify those risk alleles with specificity, but their failure to find risk alleles with large effect has contributed to the development of GWAS approaches focused on groupings of risk alleles as discussed next.

Candidate Gene Studies. As described above, genes that impart liability on monogenic neurological diseases are typically identified by linkage analysis studies. Briefly, linkage analysis studies seek to identify the link between proximate markers on a chromosome that identify the locations (loci) of genes due to their violation of Mendel's second law of independent assortment and traits that co-assort (recombine within families) with those genes in an improbably correlated manner (Knopik et al., 2017; Craig, 2012). By design, linkage analysis studies generally assume a single putative allele that imparts complete or a majority of risk on a behavioral phenotype (Hoehe et al., 2018). Consequently, use of linkage studies for polygenic disorders has proved largely unsuccessful (Hoehe et al., 2018). In contrast to linkage studies, association studies compare allelic frequencies in groups with mental disorders (behavioral phenotypes) with frequencies in neurotypical controls to identify risk alleles (Durarte et al., 2021; Knopik, 2017). As stated above, polygenic disorders have multiple risk alleles. However, to identify such risk alleles, massive amounts of genotyping are required, which, in the early

days of molecular genetics methods, was not possible or was prohibitively expensive (Knopik et al., 2017). Consequently, early studies, candidate gene association studies, focused on alleles that were *a priori* suspected to be associated with a behavioral phenotype. Such studies are discussed next generally and later in this chapter more specifically after discussion of the endophenotype literature, behavioral phenotypes, and neuropsychological measures.

Many of these candidate genes were identified by token of being implicated as targets for successful psychopharmacological interventions. For example, stimulant interventions for ADHD implicate a focus on biological targets in dopaminergic pathways (Smith, 2010). Consequently, alleles of genes that code for various such targets have served as putative candidate genes, most notably, a seven repeat polymorphic allele of the dopamine receptor D4 (DRD4-7R) discussed later in this chapter (Gizer et al., 2009; Smith, 2010). Pharmacodynamic associations form the hypothesis for their association to the behavioral phenotype a given intervention treats. However, there are relatively few candidate genes with such putative pharmacodynamic associations, and the population of candidate genes represents only 2% of DNA found in the coding regions of the genome (Knopik et al., 2017). While genetic linkage association studies were the initial methods of choice for individual allelic association, at least for monogenic disorders, candidate gene associations studies were relatively recently the state of the art for polygenic disorders (Hoehe et al., 2018).

Candidate gene studies are relatively simple and inexpensive to perform compared to other molecular genetics studies. They typically target either de novo identification of alleles associated with a particular behavioral phenotype, exploration of prognostic allelic indicators, or assessing the liability of a specific allele on a behavioral phenotype (David, 2021). It is this final category of candidate gene studies that was a key focus of this study. Specific candidates can be

single nucleotide polymorphisms (SNPs) at the DNA level or insertions or deletions at the amino acid level (i.e., nucleotide triplet combination substitutions), and structural variants (David, 2021). They can also be copy number variants (CNVs), which are duplications (repeats) or deletions of long stretches of coding and non-coding DNA sequences, such as the DRD4-7R allele discussed previously (Knopik et al., 2017). As discussed above, initially, a putative gene is identified for study from some known association to the behavioral phenotype of interest, such as psychopharmacological association with biological targets. Often, select alleles (polymorphisms) are the focus with clinical samples against neurotypical controls to identify associations between those alleles and individuals with the disorder based on pre-test genotyping of both groups. Specific candidate gene studies are discussed later in the chapter in the context of behavioral phenotypes (see sections on each behavioral phenotype that were the focus of this study) and use with neuropsychological measures (see sections discussing studies that use such measures).

Genome Wide Association Studies (GWAS). Since candidate gene studies are based on *a priori* assumptions regarding associations between candidate genes and behavioral phenotypes, they are hypothesis testing methods (David, 2021). Genome wide associations studies (GWAS) are hypothesis generating methods (David, 2021). Generally speaking, a hypothesis generation method should logically precede a hypothesis testing method. However, as mentioned above, the barriers to whole genome sequencing have prevented that logical sequence, until now. Improved technology and reduced cost of sequencing an entire genome for SNPs (or CNVs) that are common and predictably located across the whole genome have progressed to the point where studies with extremely large sample sizes are no longer cost prohibitive and enable the systematic interrogation of differences in SNP frequencies between clinical samples and

neurotypical controls to identify groups of risk alleles for a given behavioral phenotype (Ryan et al., 2022).

Genome-wide association studies (GWAS) interrogate the entire genome to identify primarily single nucleotide polymorphisms (SNPs) or CNV's, each of small effect, that collectively impart liability on a behavioral phenotype as a product of differences in their frequency distribution between clinical and neurotypical samples (Craig, 2012; Ferrera & Nurenberger, 2022; Uffelemann et al., 2021). Each individual SNP, for example, has an often statistically insignificant contribution to overall liability for a behavioral phenotype, but many such SNPs that impart correlational liability can provide a statistical association with a mental disorder (Craig, 2012; Uffelemann et al., 2021). GWAS is based on the concept of linkage disequilibrium. Linkage disequilibrium is founded on the premise that two polymorphisms that are jointly inherited more frequently than suggested by random association are likely located in close physical proximation on a gene (Craig, 2012; Uffelemann et al., 2021). GWAS, which focuses on common SNP and other polymorphic variants contrasts with whole genome studies (WGS) and whole exome studies (WES), which are focused on rare variants and not discussed here, although they are often confounded with or combined under GWAS in the literature (Uffelemann et al., 2021).

Because GWAS is a product of the very small effect individual SNPs confer on the overall liability for a behavioral phenotype, GWAS studies require massive sample sizes to achieve sufficient statistical power (Ferrera & Nurenberger, 2022; Uffelemann et al., 2021). Case control studies are common so a study must be powered for dichotomous groups of clinical and neurotypical control samples (Uffelemann et al., 2021). These sample sizes can range from the tens of thousands to hundreds of thousands, even millions, of subjects, making GWAS studies

impossible to conduct absent collaboration and consortium across many institutions and laboratories (Knopik et al., 2017).

GWAS Results, Quantitative Trait Loci, and Polygenic Risk Scores. Results from GWAS studies are typically reported via Manhattan plots of p -values and effect sizes vs. chromosomal loci (Uffelmann et al., 2021). Post hoc tests include computational statistical fine mapping to identify causal variants statistically teased out of linkage disequilibrium inferences (Uffelmann et al., 2021). Quantitative trait loci (QTL) mapping is also used to identify the location (loci) on a chromosome of alleles that impart liability on quantitative (continuous) traits, particularly for polygenic quantitative traits (Abiola et al., 2003). For determining liability for behavioral phenotypes in light of the missing heritability problem, polygenic risk scores, based on GWAS data, are particularly useful (Fisch, 2022).

Polygenic risk scores (PRS) interrogate summary statistics from GWAS studies to describe the accumulated risk (liability) of an individual for a behavioral phenotype as a product of the sum of individual risk alleles (including SNPs and CNVs) that are weighted by their effect sizes (Chatterjee et al., 2016; Fisch, 2022; Gunter et al., 2024; Martin et al., 2019; O'Connell et al., 2022). The effect size of the risk allele is typically quantified via an odds ratio as an increase in PRS by one standard deviation (Uffelmann et al., 2021). Consequently, individuals can be genotyped for a plurality of SNPs or CNVs or risk alleles implicated in GWAS studies to determine their relative risk for developing a behavioral phenotype (Chatterjee et al., 2016; Fisch, 2022; Gunter et al., 2024; Uffelmann et al., 2022). PRS has been useful for addressing the typically very small effect of individual risk alleles by combining frequency distributions (typically normal distributions) of these risk alleles between cases and controls from GWAS (Chatterjee et al., 2016; Fisch, 2022; Gunter et al., 2024; Torkamani et al., 2018).

PRS can thus be used to inform therapeutic interventions, screening and diagnosis, and prevention (Gunter et al., 2024; Torkamani et al., 2018). Coupled with the liability-threshold model discussed previously and below, PRS can be used as a quantitative diagnostic tool for differential diagnosis of mental disorders. However, it is important to note that PRS as applied to individuals are based on GWAS data of massive population samples and many PRS designs may be poor predictors of individual outcomes (Fisch, 2022; Wand et al., 2021). Although further details from the literature will not be discussed here, lack of standards for PRS methods, studies, and reporting suggest caution and careful study design (Fisch, 2022; Wand et al., 2021). The accuracy of the PRS is often a product of SNP or CNV heritability (using statistical fine mapping and QTL mapping of quantitative traits and other methods), which informs selection of risk alleles for screening, and sample size, in addition to proper study design accounting for appropriate populating sampling (Chatterjee et al., 2016; Fisch, 2022; Martin et al., 2019). Nonetheless, PRS have been useful in psychiatric genetics.

Implications of Molecular Genetics Studies, QTL, and PRS on Endophenotype Research

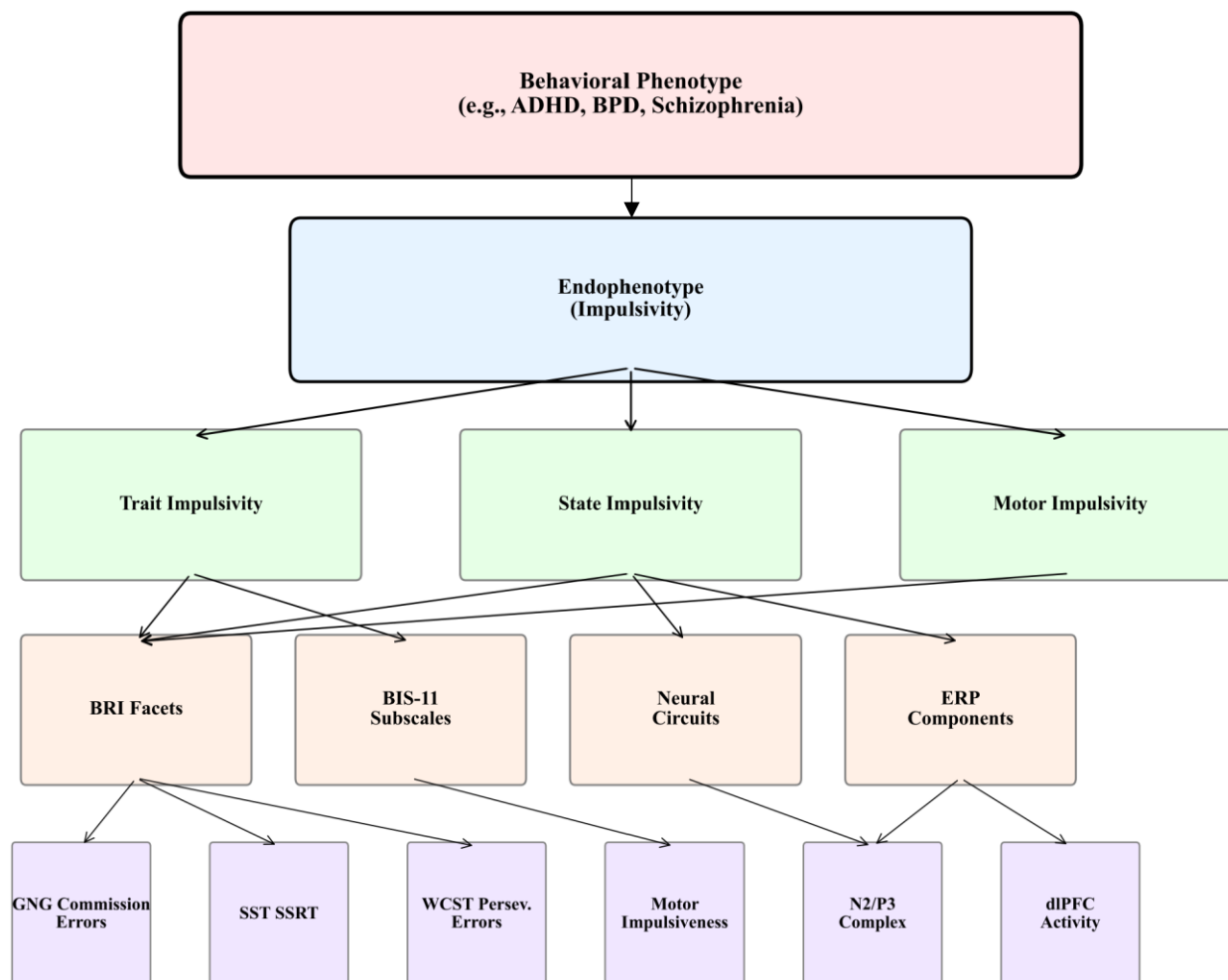
Several aspects of candidate gene, GWAS, and PRS in the context of NDST discussed previously, are key in the context of endophenotype research. First, while there are a finite number of genes, and a finite, albeit large, number of possible alleles (i.e., genotypes), there is an apparently infinite number of possible phenotypes (de Vienne, 2022). Second, “there is no limit to the number of measurable or calculable phenotypes at all levels of biological organization and over the full range of spatial and temporal scales” (de Vienne, 2022, p. 155). From an NDST perspective, this means that phenotypic determination is spatially and temporally scale agnostic. Phenotypes can exist at the molecular level or at the behavioral phenotype level and everything in between using any unit of measure in the RDoC or otherwise. Deep phenotypes may, in

theory, comprise infinite component phenotypes, and infinite component endophenotypes, which may comprise dimensionally higher deep endophenotypes, comprised of infinite component endophenotypes, suggesting an infinite multimodal multi high dimensional feature space, invoking NDST. Quantitative genetics and molecular genetics concepts can be applied across scales of phenotypic organization because most such intermediate phenotypes are also polygenic, whether express or latent (i.e., psychiatric markers or endophenotypes; de Vienne, 2022). Thus, QTL, PRS, dominance, epistasis, and quantitative and molecular heritability are useful concepts across virtually all phenotypic scales (de Vienne, 2022).

Third, a key determinant of the bounded scope of genotypes and apparently unbounded scope of phenotypes is pleiotropy (Fisch, 2022; Martin et al., 2019; de Vienne, 2022). Pleiotropy is the concept where a given allele confers risk to multiple phenotypes (Fisch, 2022; Martin et al., 2019). Consequently, PRS is sensitive to pleiotropic influence in that individual SNPs or CNVs can impart liability on multiple phenotypes and is often a problem in GWAS and PRS (Fisch, 2022; Martin et al., 2019). However, this also presents an opportunity to decompose pleiotropic relationships by scaling down or decomposing phenotypes where pleiotropic influences may be bifurcated (differentiated or dimensionalized) or at least reduced (i.e., simplified). Thus, the often-apparent conflict between reductionist and deterministic research on emergent complex systems may actually be reconciled, at least to some extent, by understanding that emergent phenomena can have reductionist etiology. This is the concept of endophenotype decomposition as illustrated in Figure 2. The above are important suppositions to consider in light of the endophenotype literature, which is discussed next.

Figure 2

Endophenotype Decomposition: From Behavioral Phenotypes to Deep Endophenotypes



Endophenotypes

Endophenotypes are intermediate phenotypes with genetic liability that can be behavioral, biological, neuropsychological, or neurophysiological, trait based or characteristic based, across spatial and temporal scales and units of measure, and are more phylogenetically proximate to the precursive genotype than a behavioral phenotype, such as ADHD or schizophrenia (Dick, 2018; Fisch, 2022; Jonas & Markon, 2014; Juli et al., 2021; Macfarlane,

2018; Meyer-Lindenberg & Weinberger, 2006; Mosconi et al., 2023; Pua et al., 2023; Ritsner & Gottesman, 2009; Tikka, 2013; Tye et al., 2011; Yorca-Ruiz et al., 2024;). Consequently, endophenotypes should be more homogenous with respect to their genotype and more tightly linked, putatively facilitating easier study and use in diagnostic inquiry of derivative behavioral phenotypes, or generally with respect to the study of personality (Dick, 2018; DiLalla et al., 2017; Donati et al., 2020; Eisenberg et al., 2007; Fisch, 2022; Iacono, 2014; Juli et al., 2021; Jonas & Markon, 2014; Meyer-Lindenberg & Weinberger, 2006; Sanchez-Roige & Palmer, 2020; Tye et al., 2011). Further, trait specific endophenotypes are often more appropriate biological and behavioral targets for the study of genetic linkages for such behavioral phenotypes (personality traits and mental disorders) as well as for neuropharmacological interventions (DiLalla et al., 2017; Eisenberg et al., 2007; Ging-Jehli et al., 2021; Iacono, 2014; Jonas & Markon, 2014; Meyer-Lindenberg & Weinberger, 2006; Tye et al., 2011).

Endophenotypes have become a focus of research to more precisely identify genetic etiologies for polygenic heterogeneous and multifactorial psychiatric disorders, personality traits, and behavioral phenotypes (Dick, 2018; Eisenberg et al., 2007; Ekin et al., 2024; Fisch, 2022; Gunter et al., 2024; Jonas & Markon, 2014; Juli et al., 2021; Macfarlane, 2018; Meyer-Lindenberg & Weinberger, 2006; Mosconi et al., 2023; Saracaydin et al., 2024; Pua et al. 2023; Ruiz et al., 2024; Tye et al., 2011; Xia et al. 2024; Yorca-Ruiz et al., 2024). Thus, endophenotypes can be used to more precisely and simply identify susceptibility genes (risk alleles) in candidate gene studies and to facilitate determination of the functional consequences of given allelic genotypes— that is, the biological etiology of a cognate behavioral phenotype, which can inform not only personality psychology, but also abnormal psychology and a DSM diagnostic regime and nosology that is phenomenological and not etiological (Chen et al., 2012;

DiLalla et al., 2017; Fisch, 2022; Macfarlane, 2018; Ritsner & Gottesman, 2009; Sanchez-Roige & Palmer, 2020; Walters & Owen, 2007).

Fundamental to the concept of endophenotype, then, is its use as a tool for understanding the biological basis of behavior or psychopathology, including nosology and diagnosis of the latter, through the linkage of genotype to behavioral phenotype via deep phenotyping (Dick, 2018; Fisch, 2022; Flint & Munafo, 2007; Gottesman & Gould, 2003; Gunter et al., 2024; Iacono, 2016; Juli et al., 2021; Krčmář et al., 2023). While phenotypes characteristically represent the observable physical or functional makeup of an organism, including the phenotypic output of the brain manifested as behavior, or particular features, such as eye color, or certain neurobiological disorders, such as monogenic forms of Parkinson's disease or Huntington's disease, genotypes define their genetic origins (Chen et al., 2012; de Vienne, 2022; Gottesman & Gould, 2003; Gunter et al., 2024; Ellenbroek, 2016; Macfarlane, 2018; Tong et al., 2024).

As described in the previous section, classical Mendelian genetics often accounts for so called monogenic phenotypes comprising behavioral characteristics, diseases, or disorders in that they derive from one genotype consequent of allelic polymorphisms in one source gene, including autosomal dominant diseases, such as Huntington's disease (Chial, 2008; Ellenbroek, 2016; Tong et al., 2024). Because monogenic disorders are derivative of genotypes comprising few (and thus rare) polymorphisms to one gene, notwithstanding that such rare alleles may cause significant deleterious effects, their prevalence in the population tends to, indeed, be rare because evolutionary theory suggests that such deleterious alleles are selected out of generational propagation, although new polymorphisms can emerge to persist the disorder or disease (Blekhman et al., 2008; Cannon & Keller, 2006; Juli et al., 2021).

Some behavioral characteristics, neurological or psychiatric diseases, or disorders, however, derive from more than one genotype (they are polygenic), including from alleles comprising polymorphisms in a plurality of genes. This polygenic etiology is made more complex and dynamical by epigenetics, which informs gene expression as a consequence of both genotypic and often stochastic environmental factors (Ellenbroek, 2016; Gottesman & Gould, 2003). Almost six decades ago, Gottesman and Shields (1967), expanding on the work of Falconer (1965), posited that schizophrenia is such a disorder. That is, Gottesman and Shields (1967) posited that schizophrenia is not a product of monogenic Mendelian genetics, but a polygenic neurobehavioral disorder subject to multiple susceptibility genes or risk alleles (genotypes) as influenced by epigenetic and other environmental factors. Thus, multifactorial polygenic behavioral phenotypes, such as schizophrenia, are at once more dynamical, and more complex, and more distal from their precursive genotypes (Donati et al., 2020; Tandon et al., 2024). Such polygenic multifactorial disorders are often hundreds, if not thousands, of times more prevalent in the population than their monogenic counterparts due, substantially, to the symphony of a plurality of compounded small effects from an array of risk genotypic alleles (Cannon & Keller, 2006; Juli et al., 2021). Thus, while a monogenic disorder consequent of a given single allelic polymorphism presents as a blunt dichotomous state for diagnosis, multifactorial polygenic disorders are consequent of far more subtle and complex allelic polymorphic and epigenetic dynamics (Juli et al., 2021). These dynamics are informed by probability theory resulting in cumulative symptomatic spectrums on a continuum of severity or frequency that capture a larger population of diagnostic categorical membership (Knopik et al., 2017). As suggested in the last section with respect to the liability-threshold model, this continuum can evolve to categorical membership when a threshold, inflection, or accumulation

of additive liability presents a dichotomous phase transition from trait to syndrome to full blown DSM diagnosis (Cannon & Keller, 2006; Knopik et al., 2017).

It is the above exponential jump to multifactorial etiology that forced an inquiry to search for simpler, though not necessarily monogenic, factors that contribute to downstream polygenic behavioral phenotypes. Psychiatric genetics, discussed in the previous section, came upon the term endophenotype as a derivative adaptation by Gottesman and Shields (1973) of the term originated by Lewis (1966), who had contrasted it with exophenotypes in that endophenotypes described phenotypes that were internal, non-obvious, microscopic, and measurable via microscopic observation or biochemical assay. Endophenotype thus became a term describing latent non-obvious non-apparent (hidden) variables comprising genetically originated intermediate phenotypes that could be used in the etiological inquiry of genotype to behavioral phenotype (Fisch, 2022; Juli et al., 2021; Sanchez-Roige & Palmer, 2020).

It took three decades, however, from the initial introduction of endophenotypes, for the research community's frustration with small effect sizes of risk alleles to behavioral phenotypes to focus the fields of molecular genetics, computational mathematics, statistical genetics, mathematical statistics, neuroimaging, and neurophysiology, alone or in combination with the developing tools of neuropsychology, to begin to offer the tools for that inquiry to the fields of psychiatric genetics and behavioral genetics in a significant and more or less reasonably precise and quantitative manner, yielding comprehensive deep phenotypes (Chen et al., 2012; Gersohn et al., 2018; Gottesman & Gould, 2003; Gottesman & Shields, 1973; Krčmář et al., 2023; Robinson, 2012). These genetically determined intermediate phenotypes (endophenotypes) could be traits or characteristics or facets that comprise, anticipate, or precede symptoms or components of clinical behavioral phenotypes, such as positive or negative symptoms of

schizophrenia, and are defined by how they are measured (applying RDoC units of analysis), including neurobiological, neurophysiological, biochemical, neuroanatomical, and neuropsychological endophenotypes (Gottesman & Gould, 2003; Ritsner & Gottesman, 2009; Juli et al., 2021; Tandon et al., 2024). Categorization of endophenotypes as “anatomical, developmental, electrophysiological, metabolic, sensory, or psychological/cognitive” has also been suggested (Flint & Munafo, 2007, p.164), which is somewhat less dependent on how they are measured. Including biochemical or metabolic processes as categorical types of endophenotypes raises a question of the role of genotype in their etiology, both absolutely and relatively. Metabolic processes, for example, do have genetic correlates, but can be substantially modulated by environmental factors, even to a greater extent than by polymorphisms in their genetic correlates (Ritsner & Gottesman, 2009), and further, measured metabolic variables can present as states, and thus, as discussed next, may be more appropriately cast as biomarkers rather than as endophenotypes.

Endophenotypes vs. Biomarkers

Endophenotypes are often considered synonymous with the term biomarker (biological marker) common in medicine and pharmacology. A biomarker is a measurable physical, chemical, or biological characteristic that indicates, references, or predicts biological processes (normal or pathogenic) or responses to pharmacological interventions (Ritsner & Gottesman, 2009; Strimbu & Tavel, 2010). However, what arguably differentiates endophenotypes from biomarkers is that the former focuses on genetic linkage, although the endophenotype literature does not always make such a distinction (Fisch, 2022; Gottesman & Gould, 2003; Ritsner & Gottesman, 2009; Walters & Owen, 2007). Some authors argue that endophenotypes are subsets of biomarkers, although generally, they distinguish endophenotypes from so called episode

markers (suggesting state dependence) and trait markers through genetic liability (Iacono et al., 2017).

At any rate, endophenotypes and biomarkers can be considered precursive to downstream clinical endpoints, behavioral phenotypes, diseases, or disorders. Endophenotypes are putative phenotypic precedents that may be broader than downstream phenotypes, in that they are pleiotropic and may tie to many phenotypes, or that may be specific to particular downstream phenotypes, when narrowly measured or characterized (Fisch, 2022; Juli et al., 2021; Sanchez-Roige & Palmer, 2020). As such, like biomarkers, endophenotypes may be more primitive, stable, and conserved than their downstream phenotypes, which, when taking genetic linkage into account, indicates that they are phylogenetically more proximate to the precursive genotypes of given downstream phenotypes (Gottesman & Gould, 2003; Juli et al., 2021; Ritsner & Gottesman, 2009; Sanchez-Roige & Palmer, 2020; Strimbu & Tavel, 2010). While even endophenotypes may be multifactorial and polygenic, and not necessarily less complex than a manifest downstream behavioral phenotype, if a given endophenotype is sufficiently differentiated, bifurcated, decomposed, deconstructed, or precisely measured, the closer proximity to genotype may suggest that a polygenic disorder or personality construct may be broken down into Mendelian-like monogenic components, which are putatively easier to study and increase the statistical significance or power or effect size of a given genotype (Fisch, 2022; Gottesman & Gould, 2003; Iacono et al., 2014; Ritsner & Gottesman, 2009; Sanchez-Roige & Palmer, 2020).

Some authors have questioned the assumption that effect sizes and statistical power of genotypes contributing to endophenotypes are larger than that of genotypes contributing to behavioral phenotypes (Fisch, 2022; Flint & Munafo, 2007; Iacono et al., 2014). However,

reports questioning this assumption often focus on particular endophenotypes, suggesting endophenotype selection, characterization, identification, or differentiation may be the issue, rather than the endophenotype concept itself, which includes identifying endophenotypes that can be subject to monogenic decomposition. Thus, monogenic decomposition may be a critical endgame in endophenotype research and was a key focus of this study, as discussed further below after discussion of endophenotype criteria and dimensional models. Again, this reductionist approach to study, characterize, and discriminate the components of endophenotypes, can also be, at once, an emergent approach to deep endophenotyping, reconciling NDST with determinism.

Criteria for Endophenotype Candidacy

Although, as mentioned above, the endophenotype literature does not always precisely limit the term to genetic linkage, thus making it more synonymous with the term biomarker. Gottesman and Gould (2003) adopted criteria from psychiatric genetics, in an effort to provide some measure of categorical framework, to classify endophenotypes as a construct that has been revised and updated over the years. Under their criteria, to qualify as an endophenotype, it must be (a) associated with a disease or disorder, (b) heritable, (c) state independent, decoupled from presence or absence of the disease or disorder and aged normed, (d) co-segregated within families, (e) found in unaffected relatives of probands at higher rates than the general population, and (f) reproducibly (quantitatively) measured (Beauchaine & Constantino, 2017; Chen et al., 2012; Gould & Gottesman, 2006; Kendler & Neale, 2010; Owens et al., 2016; Ritsner & Gottesman, 2009; Sanchez-Roige & Palmer, 2020; Walters & Owen, 2007). Pleiotropy, discussed in the previous section, has also been suggested as an additional criterion (Owens et al., 2016), as well as good psychometric properties (Walters & Owen, 2007). Both of these

additions are arguably well advised, although the concept of monogenic decomposition of endophenotypes may argue against pleiotropy being an explicit criteria.

Cannon and Keller (2006) suggested a variant set of criteria: (a) heritability, (b) association with causes and not effects of psychopathological disorders, (c) a plurality of endophenotypes should affect a given complex (multifactorial) disorder, (d) continuous endophenotypic variance in the general population, (e) optimal measurement across multiple levels of analysis, and (f) those endophenotypes implicated in multiple psychopathologies should be found for those psychopathologies that are genetically related to each other.

Jablensky (2009) summarized a broad compilation of criteria combining Gottesman and Shields' updates with additional criteria proposed by numerous authors and consortia: (a) state independence, including detectability prior to onset of DSM symptoms, (b) co-segregation within families and at least moderately heritable, (c) modest to large effect size of prevalence as compared to controls, (d) higher prevalence in family members versus general population, (e) normally distributed trait in population, (f) strong biometric or psychometric properties, (g) plausible association with genetic correlates versus consequences, (h) related to characterized neurobiological pathways and neural systems, (i) larger genotype association effect sizes than behavioral phenotype, (j) translatable into animal models, and (k) test measures should be cost effective and practicable. See Beauchaine & Constantino (2017), Flint and Munafo (2007), and Sanchez-Roige and Palmer (2020) for examples of additional criteria suggested by the literature.

Again, while the literature does not consistently apply the level of precision described in the previous paragraphs to endophenotypes, these criteria are helpful to understand the etymology and definition of the term and distinguish the term and its research from biomarker research, while providing direction and informing research to identify the most suitable

endophenotypes. While genetic linkage is described as the most important differentiator from biomarker, state independence may be next, in that endophenotypes should not be states, but rather traits, and biomarkers can be states (Beauchaine & Constantino, 2017; Iacono et al., 2014; Sanchez-Roige & Palmer, 2020). Regardless, the path from genotype to behavioral phenotype both defines and suggests a search for intermediate phenotypes along the way.

Mediational vs. Liability-Index Models

Some authors have suggested that the term intermediate phenotype is more appropriate than endophenotype, including that the latter term suggests a ‘hidden’ aspect whereas the term intermediate phenotype suggests a visible biological trait with a direct and predictable path from genotype to behavioral phenotype (Meyer-Lindenberg & Weinberger, 2006). This perspective aligns with concepts from statistical genetics and genetic epidemiology and the so-called mediational model for endophenotypes. The mediational model posits that the causal path between genotype and endophenotype is shared with the downstream behavioral phenotype and thus any modulation of the endophenotype would result in a modulation of the behavioral phenotype (Kendler & Neale, 2010). In other words, the endophenotype is an intermediate phenotype along the exclusive and direct path between genotype and behavioral phenotype and any alteration of the endophenotype also alters the behavioral phenotype.

By contrast to the mediational model, the so-called liability-index (risk indicator) model posits that genotype impacts each of endophenotype and behavioral phenotype from a pleiotropic perspective (Kendler & Neale, 2010; Walters & Owen, 2007). Thus, the liability-index model does not require that the path from genotype to behavioral phenotype pass through the endophenotype but suggests that genotype may have independent and separate paths to endophenotype and behavioral phenotype, what Walters and Owen (2007) called epiphenomenal.

Therefore, this further suggests that measurement of the endophenotype may indicate risk for (i.e., as a covariate of) the behavioral phenotype (Kendler & Neale, 2010; Walters & Owen, 2007).

The distinction between the mediational model and the liability-index (risk indicator) model thus suggests that any effort to modulate or treat the behavioral phenotype (an intervention) occurs at the endophenotype level under the mediational model and at the genotype level under the liability-index (risk factor) model (Kendler & Neale, 2010). The liability-index (risk indicator) model would appear to suggest a definition of endophenotype more similar to that of a biomarker, which is often considered synonymous to a risk factor (Ritsner & Gottesman, 2009; Strimbu & Tavel, 2010). However, some authors have suggested that endophenotype should be limited to the mediational model and the term biomarker should be used to capture the liability-index (risk indicator) model (Kendler & Neale, 2010; Sanchez-Roige & Palmer, 2020; Walters & Owen, 2007). Nonetheless, as noted above, intermediate phenotype may be more appropriate in the context of the mediational model, thus suggesting the term endophenotype be limited to the liability-index (risk indicator) model. Further, as also noted above, biomarkers have a similar assumption, leaving only genetic etiology as a necessary differentiator (and, perhaps, as suggested above, state independence). More importantly, the literature has not consistently and sufficiently discriminated these two models for bifurcation of terms to be meaningful and statistical genetics suggests that a combination of both models may operate for certain multifactorial behavioral phenotypes and/or endophenotypes (Kendler & Neale, 2010; Walters & Owen, 2007).

Thus, the term endophenotype was used in this study to include any distinct notion of the term intermediate phenotype or any implicit or explicit assumption regarding whether statistical

genetic path analysis from genotype to behavioral phenotype suggests the mediational or the liability-index (risk indicator) models but distinguished from the term biomarker in light of genotypic etiology (and potentially state independence). However, it should be noted that environmental endophenotypes (environmental risk factors), would not require a genetic correlate and even given endophenotypes may be loaded by both genotypic and environmental risk factors (Kendler & Neale, 2010; Walters & Owen, 2007).

Endophenotype Typing and Decomposition

In the continuum from genotype to behavioral phenotype, endophenotypes can arise directionally or proximately. The path or paths from neurobiological genotype to behavioral phenotype passes through intermediate phenotypic destinations found in the RDoC matrix comprising proteins and protein expression, cellular constructs and systems and signaling pathways, neural networks, cognitive functional systems, and finally to symptomology that, when mixed just so, manifests as behavioral phenotype (Cannon & Keller, 2006; Sanchez-Roige, 2020). With such a vast range of potential endophenotypes across multiple dimensions and RDoC units of analysis, it is impossible to summarize the full range of endophenotype studies in one literature review. This study focused on a narrower range of neuropsychological, neurophysiological, and neurobiological endophenotypes related to impulsivity and BRI. Consequently, the study of the endophenotype literature in that narrow area will be discussed after introduction of those concepts and related general literature. However, some synthesis and integration of the discussion on psychiatric, behavioral, quantitative, and molecular genetics from the prior section is appropriate with this section on endophenotypes.

Iacono et al. (2014) reviewed seven molecular genetics studies of 17 neurophysiological and neuropsychological endophenotypes that the authors referred to as psychophysiological in a

sample of 4,900 individuals. The authors studied both the quantitative heritability, using twin and adoption methods, and the molecular heritability, using SNP heritability GWAS methods, of each endophenotype (Iacono et al., 2014). The endophenotypes studied by the authors included several related to this study, namely, EEG P3 amplitude (discussed later in this chapter) and prepotent inhibitory control (the latent variable) via an antisaccade task (the neuropsychological unit of measure/analysis; Iacono et al., 2014). EEG related endophenotypes displayed very high quantitative heritability, but very low molecular heritability, pointing to substantial missing heritability (Iacono et al., 2014). For example, P3 amplitude had about 60% quantitative heritability and 28% molecular heritability while antisaccade inhibitory control had about 59% and 57% respectively (Iacono et al., 2014).

Iacono et al. (2014) made several observations that were informative for this study and provided useful inferences. First, somewhat contrary to the endophenotype hypothesis, as was suggested by Flint and Munafo (2007), polygenic heritability of endophenotypes is not necessarily simpler than for a related upstream behavioral phenotype. Second, the larger the missing heritability, the fewer risk alleles are known, since such alleles remain latent. Third, studies that focus on over selecting samples at the extremes for each endophenotype may improve results to identify candidate endophenotypes (or deep endophenotypes). This inference influenced the sampling and study design for this study. Fourth, for endophenotypes to achieve their potential as alternative targets for behavioral phenotypes, a balance must be achieved between given effects of each risk allele and sample size to optimize power to detect smaller effects.

The fourth inferential observation in the previous paragraph from Iacono et al. (2014) suggests decomposing endophenotypes to find a narrower set of risk alleles each with

fractionally greater effect. For example, Ford (2014) suggested parsing the P3 endophenotype into its decomposed component parts that may be more genetically tractable as “endophenotypes for endophenotypes” (Ford, 2014, p.1344), yielding what this study refers to as deep endophenotypes. P3 (P300) is discussed in more detail later in this chapter and is relevant to this study in that it represents a related endophenotype to those of this study in that it is implicated in behavioral response inhibition as well as in impulsivity as an externalizing behavior in behavioral phenotypes, such as schizophrenia and ADHD (Ford, 2014; Hilger et al., 2020; Özkan et al., 2023). Thus, Ford (2014) and Miller and Rockstroh (2013) are among those who suggest that decomposing endophenotypes can lead to stronger candidate endophenotypes. For example, the construct of executive function is a putative endophenotype for schizophrenia (Miller & Rosckstroh, 2013; Tandon et al., 2024). However, executive function is a complex construct that can be decomposed into its constituent factors, facets, or features, each putative endophenotypes (deep endophenotypes) in their own right (Miller & Rosckstroh, 2013; Sanchez-Roige & Palmer, 2020). This study represented one such attempt for neuropsychological and neurobiological endophenotypes of behavioral response inhibition, which, as discussed previously, is a condition precedent to proper engagement of executive functions. The goal of such decomposition was to better inform the ultimate goal of endophenotype research: to identify risk alleles for a behavioral phenotype, by way of risk alleles for the endophenotype, and to identify the functional consequence of such risk alleles (Miller & Rockstroh, 2013). In the case of this study, endophenotypes for deficits in behavioral response inhibition can tie risk alleles to differential expressions of functional impulsivity for behavioral phenotypes. Impulsivity and behavioral response inhibition are discussed in the next section.

Impulsivity

Impulsivity can be described as a highly heritable stable personality trait or a dynamic state that comprises an urge to act (i.e., an impulse towards motor activity) and a lack of behavioral response inhibition to suppress the urge (Beauchaine et al., 2017; DeYoung & Reuter, 2016). Impulsivity is a multifactorial construct that has a plurality of definitions in the literature. For example, impulsivity has been described as (a) behavior absent adequate thought (International Society for Research on Impulsivity, n.d., para. 1), (b) a tendency to act on a whim in disregard of more rational long term success strategies, in effect discounting a delayed reward (delayed discounting) as a decaying progression and function of time (Madden & Bickel, 2010); (c) impatience and inability to delay gratification (Green & Myerson, 2010), (d) actions that are premature, risky, poorly conceived, contextually inappropriate and result in undesirable outcomes (Moeller et al., 2001); (e) a personality trait or construct that is characterized by an urge to act spontaneously without reflecting on the consequences of the action (Coutlee et al., 2014), (f) “the tendency to act on immediate urges, either before consideration of possible negative consequences or despite consideration of likely negative consequences” (DeYoung & Reuter, 2016, p. 348), (g) a tendency to deliberate less than a comparably able person before taking action (Dickman, 1990), (h) lack of self-control (DeYoung & Reuter, 2016), (i) predisposition toward rapid, unplanned responses to internal or external stimuli absent regard for negative consequences of such responses (International Society for Research on Impulsivity, n.d., para. 1); (j) a characteristic or trait comprising acting on the spur of the moment ignorant of the risks involved (Eysenck et al., 1984; Eysenck & Eysenck, 1977), (k) an impulse, its behavioral expression, and the situation in which both occur (Coles, 1997); (l) “styles of acting and making decisions with limited foresight and a proneness to errors” (Tzagarakis, 2022, p. 01);

(m) a heterogeneous cluster of lower-order traits comprising impulsivity, sensation seeking, risk-taking, novelty seeking, boldness, adventuresomes, boredom susceptibility, unreliability, and unorderliness (Depue & Collins, 1999); (n) the inability to (i) evaluate a stimulus completely prior to responding to it (rapid response impulsivity), and (ii) delay responding to the stimulus despite a larger reward (reward-delay impulsivity; Swann et al., 2009); (o) the propensity to act absent capacity to adapt in context (Moeller et al., 2001), (p) the tendency to act or respond thoughtlessly or too hastily, seeking out immediate gratification sacrificing long term gains, and difficulty inhibiting actions (Hammond et al., 2012), (q) “premature action and decreased inhibition in response to distractions or rewarding stimuli” (Guo et al., 2017, p. 26), and (r) “a stable behavioral pattern associated with rapid and unplanned reactions to various external and internal stimuli” (West et al., 2024, p. 2).

The many disparate definitions of impulsivity in the literature illustrate its multidimensional nature. There is also great disagreement, if not controversy, in the literature regarding these definitions, with many in the research community arguing that numerous such definitions or their elements are orthogonal and poorly correlate to each other (Cyders, 2015). However, such definitions arguably capture impulsivity’s multifactorial types, sub-constructs, facets, features, levels, dimensions, components, lower order factors, and subsets. Each may be viewed as endophenotypes to the extent they have a neurogenetic correlate. Certain components, elements, or facets of the definitions of the construct of impulsivity in the previous paragraph may also represent distinct orthogonal types of impulsivity that are sub-constructs or constructs in their own right, or facets of those sub-constructs. The sub-constructs include trait impulsivity, state impulsivity, choice impulsivity, motor impulsivity, attentional impulsivity, non-planning impulsivity, and cognitive impulsivity and are discussed below. For example, choice impulsivity

and rapid-response impulsivity (i.e., motor impulsivity) have been suggested as sub-constructs of impulsivity that are present in ADHD and help distinguish impulsivity in ADHD versus impulsivity in other DSM disorders (Cyders, 2015; Patros et al., 2016).

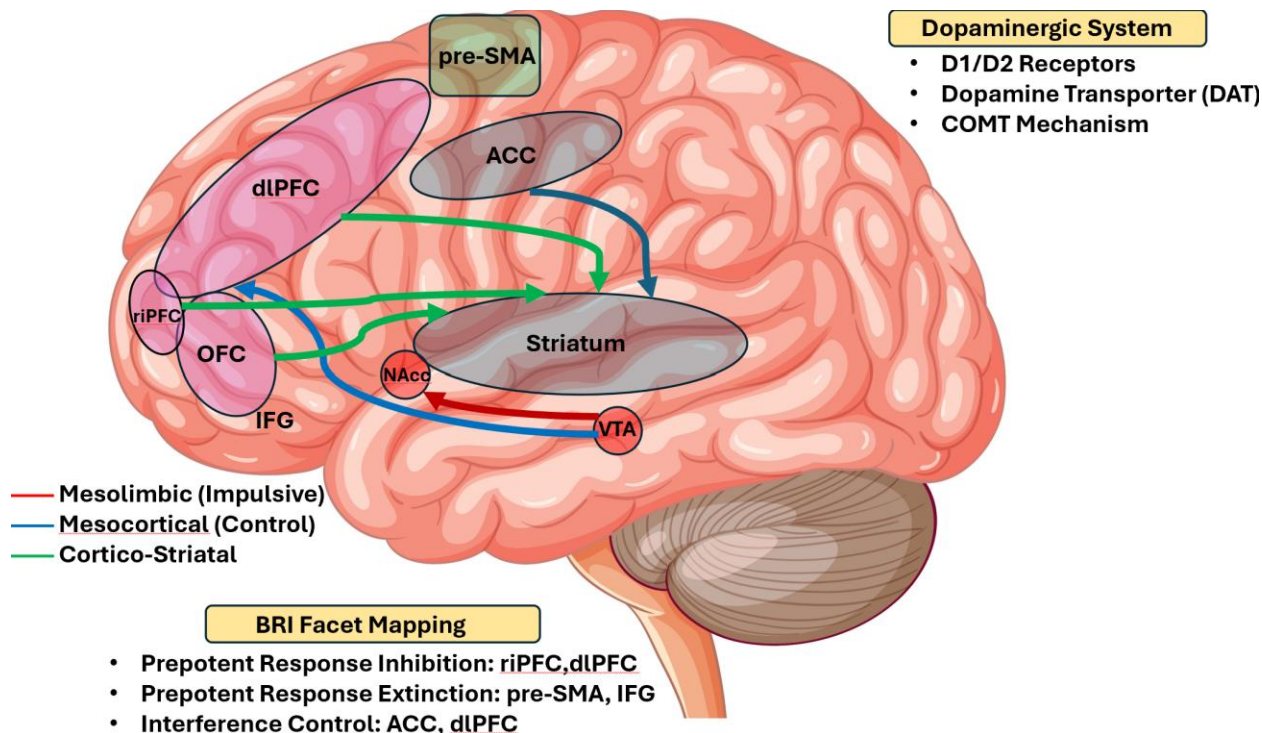
All the above suggests that impulsivity, as an endophenotype, may be decomposed into a plurality of more discriminate endophenotypes that comprise it, resulting in deep endophenotypes of impulsivity. At another dimension of analysis and measurement, each endophenotype (as a subconstruct, component, factor, facet, feature) of impulsivity, may be measured by proxy using a plurality of units of analysis (including those of this study) under the RDoC that can each also comprise endophenotypes. This suggests that deep endophenotypes of impulsivity may co-exist across numerous dimensions, and impulsivity as an endophenotype may co-exist with a plurality of other endophenotypes of a behavioral phenotypes measured across the same units of analysis, some of which may tie to impulsivity or directly to the downstream behavioral phenotype. In the end, a plurality of deep phenotypes of a behavioral phenotype may be identified, that may or may not map onto the many possible symptomatic combinations, including magnitude of expression or manifestation of given symptoms, in the DSM. All of the above is ripe for interrogation via the tools of AI enabled neurocomputational modeling, both via supervised machine learning models and unsupervised deep neural network models discussed at the end of this chapter.

Many definitions of impulsivity include the concept of negative consequences. However, while impulsivity is generally considered at the heart of dysfunction and the most common criterion symptom of psychopathology in the DSM (Cyders, 2015; DeYoung & Rueter, 2016), it need not always be considered a dysfunction when temporal constraints or considerations derisk lack of premeditation and precognition. In other words, when the temporal benefits conveyed by

skipping premeditation or precognition outweigh the risks, such that prepotency, automata, or habit may reduce those risks, impulsivity is functional and choice optimal rather than dysfunctional and suboptimal. This type of impulsivity has been termed as functional impulsivity by Dickman (1990), as opposed to dysfunctional impulsivity present in psychopathology.

Consequently, for the purposes of this study, a neutral definition of impulsivity may define impulsivity simply as behavior without forethought. Such a definition does not place a value judgment on the desirability of the behavior but does categorize it as lacking a cognitive moment to evaluate the response as a condition precedent to responding to the internal or external stimulus. This definition does conflict with some definitions that include as impulsive some non-rapid decisions with deliberation (e.g., choice impulsivity) that are contrary to logic or consideration of risks, such as that proffered by DeYoung and Reuter (2016). It appears, however, that, as discussed previously, such decisions are based on separate neural processes than impulsivity as defined here.

The process of precognition and premeditation enlists dopaminergic mesocortical circuits projecting from the medial ventro tegmental area (VTA) of the limbic system to the prefrontal cortex and thus engage prefrontal cortical executive functions that are dormant with actions without precognition and premeditation, which rely on mesolimbic circuits projecting from the VTA to the ventral striatum, primarily the nucleus accumbens (NAcc) and consequent limbic reactions (Kabanova et al., 2015; Reneaux et al., 2015). These neural network systems underlying BRI are illustrated in Figure 3. Engagement of different neural networks suggests the possibility of differential endophenotypes to represent them.

Figure 3*Neural Network Systems Underlying Behavioral Response Inhibition*

Note: dIPFC = dorsolateral prefrontal cortex, OFC = orbitofrontal cortex; riPFC = right inferior prefrontal cortex, IFG = inferior frontal gyrus, pre-SMA = pre-supplementary motor area, ACC = anterior cingulate cortex, NAcc = nucleus accumbens, VTA = ventral tegmental area.

Background brain image by brgfx on Freepik. Circuit mapping by John Wehrli.

Impulsivity vs. Compulsivity

Impulsivity is also often considered at the opposite extreme of the continuum from impulsivity to compulsivity, with the two even orthogonal to each other (Dück et al., 2023; Guo et al., 2017; Hook et al., 2021; Fineberg et al., 2014; Moeller et al., 2001; Naguy & Naguy, 2022; Sanchez-Kunh et al., 2017). However, they are also arguably positively correlated (Dück et al.,

2023). Like impulsivity, compulsivity is a multifactorial construct. It can be defined as “a behavioral ‘stickiness’ with an abnormal perseveration on actions and strategies that are often maladaptive” (Tzagarakis, 2022, p.1), as a “loss of control over goal-directed behavior” (Demetrovics et al., 2022, p.2), as repetitive acts under subjective loss of control (Dück et al., 2023), as “a tendency towards repetitive, habitual actions, which an individual feels compelled to perform, and are repeated despite adverse consequences” (Hook et al., 2021, p. 455), as “the performance of repetitive and functionally impairing overt or covert behavior without adaptive function, performed in a habitual or stereotyped fashion, either according to rigid rules or as a means of avoiding perceived negative consequences” (Fineberg et al., 2014, p. 2), or as “an internal urge to perform a specific but repeated act to avoid or reduce perceived harm” (Guo et al., p. 26). However, while each of impulsivity and compulsivity is considered to occur due to deficits in different corticostriatal neural network circuitry, both merge at deficits in behavioral response inhibition (disinhibition; Guo et al, 2017; Demetrovics et al., 2022; Dück et al., 2023; Fineberg et al., 2014; Naguy & Naguy, 2022; Sanchez-Kuhn et al., 2017). The merger of two orthogonal, yet arguably correlational, constructs at BRI highlights the potential for BRI and its facets as putative endophenotypes.

Impulsivity is often considered reward driven and compulsivity relief driven (Demetrovics et al, 2022; Guo et al., 2017). They are also considered risk-seeking (impulsivity) and harm-avoiding (compulsivity; Fineberg et al., 2014). Indeed, each often present as co-morbid intra-disorder deficits within several DSM mental disorders, including autism spectrum disorder and ADHD (Naguy & Naguy, 2022; Tzagarakis, 2022) and in addictive behavior disorders, such as gambling disorder, internet addiction, compulsive shopping, sex addiction, porn addiction, eating disorders, substance addiction, alcoholism, and trichotillomania (Demetrovics et al., 2022;

Flessner et al., 2012; Sanchez-Kunh, 2017). In such disorders, impulsivity and compulsivity may occur at opposite extremes of the addictive cycle (Demetrovics et al., 2022; Flessner et al., 2012).

Impulsivity-compulsivity related deficits also often result in co-morbid inter-disorder deficit occurrences, such as between ADHD and autism spectrum disorder (ASD; disorders with impulsivity as core deficits) and Tourette syndrome (TS) and obsessive-compulsive disorder (OCD; disorders with compulsivity as core deficits; Tzagarakis, 2022; Yang et al., 2021). GWAS studies have suggested factorial overlap among these and numerous other impulsive and compulsive disorders (Yang et al., 2021). In one meta-analysis of 93,294 nonoverlapping samples, Yang et al. (2021) conducted a SNP-GWAS meta-analysis of TS, ADHD, ASD, and OCD, which included studying pleiotropic effects. The authors identified several common genetic loci across those disorders.

Since disinhibition (deficits in behavioral response inhibition) lies at the nexus of impulsivity and compulsivity, BRI and its facets may serve as putative differential endophenotypes (deep endophenotypes) of either impulse control disorders and compulsivity disorders under the mediational index model and liability index models discussed in the previous section. Numerous studies have evaluated BRI in the context of impulsivity and compulsivity. For example, as discussed previously, the go/no-go task (GNG) is often considered a key unit of analysis (measure) for prepotent response inhibition, a facet of BRI. Sanchez-Kuhn et al. (2017) used the GNG to study BRI in concert with the Barratt Impulsiveness Scale (BIS-11), a self-report measure that measures trait motor impulsiveness, cognitive impulsivity, and non-planning impulsivity; and the Maudsley Obsessional Compulsive Questionnaire (MOCI) self-report measure. As mentioned previously, the literature has shown poor correlation between self-report measures, such as the BIS-11, and laboratory behavioral measures, such as the GNG task

(Barnhart & Beulow, 2017; Reynolds et al., 2006). Indeed, Sanchez-Kuhn et al. (2017) supported that observation in the literature and concluded that there was virtually no relationship between BIS-11 results and GNG prepotent inhibition in a sample of 63 neurotypical participants. However, Sanchez-Kuhn et al. (2017) did find a relationship between the GNG and the MOCI, a compulsivity self-report measure.

One can synthesize the surprising results of Sanchez-Kuhn et al. (2017) with the above observation that impulsivity and compulsivity merge at deficits in behavioral response inhibition. The BIS-11 measures primarily trait motor impulsivity. Motor impulsivity is a higher order construct of which a deficit in BRI is a facet. The MOCI also measures a higher order construct of which a deficit in BRI is a facet. The GNG task focuses on BRI. At the top level (factor) of its measure of prepotent response inhibition, it may not discriminate motor impulsivity as well as it does compulsivity. However, in light of other literature discussed in this chapter, it does have a relationship to impulsivity, perhaps more specifically as to its lower order facets (factors). Improvement of the ability of neuropsychological measures to discriminate facets of BRI and associate those measures with self-report measures of impulsivity or compulsivity may help identify decomposed endophenotypes (deep endophenotypes) that are useful in discriminating both impulsivity and compulsivity and their downstream behavioral phenotypes. They can also improve differential diagnosis of impulsive and compulsive disorders. This provides another aspect this study informed. Behavioral response inhibition is a more fundamental marker of both impulsivity and compulsivity and their dysfunctional maladaptive manifestations.

Dysfunctional Impulsivity

As stated above, impulsivity is generally considered in light of its negative consequences (dysfunctional impulsivity) and is a core symptom of many neurological and DSM

developmental and psychiatric disorders and the most common criterion symptom in the DSM entirely (Cyders, 2015). Among neurological disorders, it is a core symptom in Parkinson's disease (consequential of treatment with dopamine agonists) with or without co-morbid impulse control disorders (Dawson et al., 2023; Edelstyn et al., 2023; Faouzi et al., 2022; Giovannelli et al., 2023; Nobela et al., 2014; Spencer & Anderton, 2024; Vela et al., 2016). Among Axis I DSM disorders, impulsivity is a core symptom in bipolar disorder (Chan et al., 2023; Moeller et al., 2001), both as to manic episodes and depressive episodes (Sanches et al., 2014; Swann et al., 2008); major depressive disorder (Crisp & Grant, 2024; Sanches et al., 2014; Swann et al., 2014), and obsessive-compulsive disorder (Crisp & Grant, 2024; Xu et al., 2021). Impulsivity is also a core symptom in substance abuse disorders (Grant & Chamberlain, 2014; Mei et al., 2015; Moeller et al., 2001; Verdejo-Garcia & Albein-Urios, 2021), alcoholism (Rubio et al., 2008); behavioral disorders including gambling disorder, kleptomania, compulsive buying, and internet addiction (Coccaro & Grant, 2017; Crisp & Grant, 2024; Grant & Chamberlain, 2014), eating disorders (Crisp & Grant, 2024; Malorqui-Bague et al., 2020); pyromania (Crisp & Grant, 2024; Coccaro & Grant, 2017), and trichotillomania (Crisp & Grant, 2024; Flessner et al., 2012). Finally, impulsivity is a core symptom in disruptive and impulse control disorders (Crisp & Grant, 2024; Hook et al., 2021; Lochman & Matthys, 2017), oppositional defiant disorder (Basnal, et al., 2024; Burke et al., 2017; Crisp & Grant, 2024), conduct disorder (Crisp & Grant, 2024; Frick & Wall Myers, 2017), and intermittent explosive disorder (Coccaro & Grant, 2017; Crisp & Grant, 2024).

Indeed, impulsivity has been suggested to be the key feature of all externalizing disorders (Beauchaine et al., 2017). Externalizing disorders have an extremely high rate of comorbidity and cooccurrence that is consistent with the RDoC's transdiagnostic perspective of

neurobiological liability (Beauchaine et al., 2017). In other words, from an RDoC perspective, variation in impulsivity, whether by token of magnitude or variation in its facets, components, factors, or features, accounts for covariation among DSM disorders that implicate it (Beauchaine et al., 2017). While impulsivity is clearly central to a plurality of DSM disorders, its magnitude and its negative consequences are particularly pronounced in certain Axis I and Axis II mental disorders with high dysfunction and/or with high prevalence. Impulsivity in four such disorders is discussed next. The four disorders discussed below and later in this chapter in detail were a core focus of this study.

Impulsivity in ADHD. Perhaps no other DSM mental disorder is considered more synonymous with impulsivity than attention deficit hyperactivity disorder (ADHD). Impulsivity is particularly central to two of its three subtypes, namely, predominantly hyperactive-impulsive (H-I) type and combined type (i.e., H-I type in combination with predominantly inattentive type; Basnal et al., 2024; Beauchaine et al., 2017; Crisp & Grant, 2024; Ditrach et al., 2021; Doroldi et al., 2024; Gokce et al., 2017; Hook et al., 2021; Patros et al., 2016; Sharma & Couture, 2014; Winstanley et al., 2006). Impulsivity is often the key diagnostic marker, present in children, for example, that results in referrals for clinical evaluation and diagnosis (Gleason & Humphreys, 2016; Gokce et al., 2017; Patros et al., 2016).

However, ADHD is often co-morbid with other DSM disorders that have impulsivity as a core feature. Such disorders include oppositional defiant disorder and major depressive disorder (Basnal et al., 2024; Gomez et al., 2022; Pliszka, 2009; Sharma & Couture, 2014), conduct disorder and anxiety disorder (Pliszka, 2009; Sagvolden et al., 2005). They also include bipolar disorder, obsessive compulsive disorder (OCD), and autism (ASD), discussed below, where, prior to the DSM-V, ADHD and ASD could not be diagnosed in the same patient and since then,

comorbidity of ADHD and ASD ranges from 37%-85% (Harkins et al., 2022; Hlavata et al., 2018; LaBianca et al., 2021; Pliszka, 2009; Shin et al., 2023; Waldren et al., 2024). Finally, ADHD is also often comorbid with schizophrenia, discussed below (Gough & Morrison, 2016; Levy et al., 2015; Tossell et al., 2004), and borderline personality disorder, discussed below, where 30%-50% of BPD patients have co-morbid ADHD (Ditrich et al., 2021; Linhartova et al., 2019; Waite et al., 2024).

Consequently, the above symptomatic overlap across disorders often results in misdiagnosis, underdiagnosis, or over diagnosis of ADHD (Chilakamarri et al., 2011; Ginsberg et al., 2014; Fresson et al., 2019). This suggests that impulsivity, including the operational dysfunction of motor impulsivity, a deficit in behavioral response inhibition (lack of impulse control), may also be a key diagnostic marker across these disorders, and its facets may be distinct diagnostic markers (and endophenotypes, including deep endophenotypes, to the extent of their genetic liability) for each disorder. In other words, while the common thread of impulsivity across a plurality of DSM disorders may make differential diagnosis more difficult, if deficits in impulse control can be decomposed to unique diagnostic markers or endophenotypes (deep endophenotyping) to increase their dimensionality, they may help improve differential diagnosis. Such was one of the goals of this study. ADHD is discussed in detail later in this chapter.

Impulsivity in Autism. Unlike with ADHD, impulsivity is not always considered a seminal deficit of autism (autism spectrum disorder, [ASD]), where the classic dysfunction is typically focused on communication, social interaction, and compulsive behaviors (Hlavata et al., 2018). However, as discussed previously, impulsivity and compulsivity are often considered two sides of the same coin that merge at deficits in behavioral response inhibition. A product of

that merger is that ASD and ADHD are often comorbid (Guo et al., 2024; Shin et al., 2023; Waldren et al., 2024). Consequently, deficits in behavioral response inhibition (lack of impulse control/lack of inhibitory control) are considered a central executive dysfunction of ASD (Hlavata et al., 2018; Schmitt et al., 2019; Velasquez et al., 2017). These deficits lead to marked impulsivity among the ASD population that have very negative consequences resulting from emotional dysregulation, self-injury, impulsive anger or aggression, and a form of cognitive impulsivity commonly seen in ASD patients, particularly those with Asperger's type, where they cannot inhibit their own perspective or point of view in favor of consideration of another person's perspective (Hlavata et al., 2018; Martin et al., 2024; Uzefovsky et al., 2016). For example, Uzefovsky et al. (2016) studied a large sample of 627 subjects comprising ASD patients and controls using an on-line version of the go/no-go (GNG) task. The authors observed significantly elevated commission and omission errors in the GNG for the ASD sample, indicating a marked dysfunction of the prepotent response inhibition facet of behavioral response inhibition in this group (Uzefovsky et al., 2016). Further, the WCST measures, among other things, high perseverative errors linked to anxiety reducing compulsive behaviors, which can lead to change intolerance and, thus, impulsive aggression (Martin et al, 2024). This helps illustrate the interactions between measures in the GNG, SST, and WCST as they relate to dopaminergic impulsivity. Autism is discussed in detail later in this chapter.

Impulsivity in Schizophrenia. Where ADHD may be considered the poster child of impulsivity, schizophrenia may be considered the poster child of severe mental illness (Xavier, 2019). The dysfunction of schizophrenia is both extreme and broad (Schaefer et al., 2013). While broad cognitive dysfunction, including psychotic delusions and hallucinations, is often considered the central dysfunction of schizophrenia, it is the motor manifestation of that

cognitive dysfunction (observable operationalization of externalizing positive symptoms), via impulsive behaviors due to deficits in behavioral response inhibition, that is central to the cognitive dysfunction, as a deficit in BRI is the operational embodiment of the severe cognitive dysfunction in schizophrenia (Enticott et al., 2008; Ethridge et al., 2014; Gao et al., 2024; Hjell et al., 2023; Hoptman et al., 2018; Juričková et al., 2023; Lau et al., 2022; Nanda et al., 2016; Ouzir, 2013; Vanova et al., 2023). Consequently, impulsivity is arguably the core deficit of schizophrenia (Ouzir, 2013) and most often associated with its schizophrenia's positive symptoms (Lau et al., 2022).

Indeed, so severe is impulsivity in schizophrenia that deficits in BRI resulting in impulsivity are greater in schizophrenia than in ADHD (Hoptman et al., 2018). This dysfunction often results in externalized impulsive anger, aggression, violence, and internalized suicidal behavior as patients with schizophrenia react with motor action to their psychotic delusional episodes, hallucinations, and paranoia with want of forethought (Gao et al., 2024; Hoptmann et al., 2018; Juričková et al., 2023; Lau et al., 2022; Ouzir, 2013). The greater the level of impulsivity in a schizophrenic patient, the more severe the disorder is coded by clinicians, and the more intensive hospital and psychopharmacological interventions used (Nanda et al., 2016). Consequently, a deficit in BRI is a significant putative endophenotype for schizophrenia (Ettinger et al., 2018). Schizophrenia is discussed in detail later in this chapter.

Impulsivity in Borderline Personality Disorder. Among personality disorders, impulsivity is particularly central to the Cluster B (dramatic-erratic) personality disorders and is considered a core personality trait in the DSM-5 alternative model for personality disorders, particularly borderline personality disorder (BPD; Hamilton et al., 2015; Lombardo et al., 2023; Ruocco et al., 2021; Sellbom et al., 2017; Turner et al., 2017; Vanwoerden & Stepp, 2022; Waite

et al., 2024; Wojciechowski, 2021). For example, impulsivity is central to Cluster B antisocial personality disorder (APD) and narcissistic personality disorder (NPD; Moeller et al., 2001; Sellbom et al., 2017; Turner et al., 2017). However, even more so than APD and NPD, among the Cluster B personality disorders, impulsivity is largely considered to be both the core clinical dysfunction and primary diagnostic marker of BPD as well as its key prognostic marker over time (Gunderson et al., 2018; Jacob et al., 2009; Linhartova et al., 2019; Links et al., 1999; Lombardo et al., 2023; Mitolo et al., 2024; Moeller et al., 2001; Mungo et al., 2020; Ruocco et al., 2021; Sebastian et al., 2013; Sellbom et al., 2017; Soloff et al., 2017; Svaldi et al., 2012; Waite et al., 2024; Wojciechowski, 2021). While, arguably, impulsivity is most often associated with ADHD, impulsivity in BPD is considered more severe than in ADHD (Cackowski et al., 2014; Linhartova et al., 2019; Mungo et al., 2020; Waite et al., 2024; Wojciechowski, 2021) as well as in other Axis I disorders where impulsivity is considered a seminal deficit, such as bipolar disorder (Wilson et al., 2007). Borderline personality disorder, including impulsivity's and BRI's role in BPD, is discussed in detail later in this chapter.

Impulsivity Measures

Consistent with impulsivity's multidimensional nature, the literature describes many different measures of impulsivity, with each measure a potential endophenotype and component of a deep endophenotype of impulsivity. These can be split into neuropsychological self-report measures of trait impulsivity and behavioral (laboratory) measures of state impulsivity (Hook et al., 2021). However, there are also putative neurobiological measures of impulsivity (Congden & Canli, 2005; Mitchell & Potenza, 2014). Self-report measures are the most common measures of impulsivity in clinical settings as a symptom of DSM mental disorders (Hook et al., 2021), while laboratory behavioral measures are more common in research settings (Hook et al., 2021). These

categories of measures are briefly discussed separately below to provide enough background and context for discussions of studies in the rest of this chapter that use these various measures in the literature.

Self-Report Trait Measures. There are a large number of self-report measures of impulsivity. Each measures (or purports to measure) different individual or groups of types, facets, components, factors, features, and subtypes of impulsivity. Each of 20 self-report neuropsychological measures is briefly discussed below roughly in order of their use and validity or recognition in the literature.

Table 1

Comparison of Major Self-Report Impulsivity Measures

Measure	Items	Primary Factors	Reliability (α)	Clinical Use
BIS-11	30	Motor, Attentional, Non-planning	.81-.83 ^a	High
UPPS-P	59	Negative Urgency, Positive Urgency, Sensation Seeking	.84-.95 ^b	High
IVE-7	54	Impulsiveness, Venturesomeness, Empathy	.77-.84 ^c	Moderate
NEO-PI-R	240	Neuroticism facet (Impulsiveness)	.86-.95 ^d	High
DII	23	Functional, Dysfunctional	.85-.87 ^e	Moderate
BIS/BAS	24	Behavioral Inhibition, Behavioral Activation	.74-.76 ^f	Moderate
BDEFS	19	Self-restraint/ Inhibition	.91 ^g	Moderate

Measure	Items	Primary Factors	Reliability (α)	Clinical Use
SSS-V	40	Disinhibition, Experience Seeking	.83-.86 ^h	Moderate
EASI-III	20	Inhibitory Control, Decision Time, Sensation Seeking, Persistence	.75-.82 ⁱ	Low
ICBC	33	Impulsivity, Compulsivity, (Dual factors)	.89-.92 ^j	Moderate

^a (Patton et al., 1995), ^b (Lynam et al., 2006), ^c (Eysenck et al., 1985), ^d (Costa & McCrae, 1992),
^e (Dickman, 1990), ^f (Carver & White, 1994), ^g (Barkley, 2011), ^h (Zuckerman et al., 1978), ⁱ
 (Buss & Plomin, 1975), ^j (Guo et al., 2017).

Barratt Impulsiveness Scale (BIS-11). The 30 question Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995) was selected for this study and is discussed in detail in Chapter 3. It is arguably the most widely used, researched, and validated self-report measure of impulsivity (Barnhart & Beulow, 2017; Hook et al., 2021; Meule, 2023; Verdejo-Garcia & Albein-Urios, 2021). It primarily measures higher order factors of trait motor impulsiveness, attentional impulsiveness, and non-planning impulsivity and six lower order factors (components or facets) of each (Patton et al., 1995). There is a shortened 15 question version (BIS-15; Spinella, 2007) that measures the three higher order factors only, and a brief eight question version (BIS-Brief; Steinberg et al., 2013) that only measures the single factor of trait impulsivity, the overarching construct of the three higher order factors and six lower order factors of the BIS-11. A 13-question abbreviated impulsiveness scale (ABIS) was developed using the BIS-11 and measures the same higher order factors (Coutlee et al., 2014).

UPPS Impulsive Behavior Scale. The 59 question UPPS impulsive behavior scale (UPPS-P; Lynam et al., 2006) is arguably as widely used, researched, and validated as the BIS-11, if not more so (Barnhart & Beulow, 2017; Hook et al, 2021; Rogers et al., 2021; Verdejo-Garcia & Albein-Urios, 2021). It measures negative urgency, positive urgency, sensation seeking, lack of premeditation, and lack of perseverance (Whiteside & Lyman, 2001). There is also a 45 question UPPS-R version (Whiteside & Lynam, 2001) and a short 20 question version (S-UPPS-P; Cyders et al., 2014).

Eysenck's Impulsiveness Venturesomeness and Empathy (IVE-7). The 54 question Eysenck's impulsiveness, venturesomeness, and empathy scale (IVE-7; Eysenck et al., 1985) is one of the oldest and most commonly used measures of impulsivity. It measures the above three factors including impulsivity. It is often combined with other measures to study impulsivity in clinical populations, such as in the prediction of violence in schizophrenia (Kristof et al., 2018).

NEO-Personality Inventory-Revised (NEO-PI-R). The 240 question NEO-personality inventory revised (NEO-PI-R; Costa & McCrae, 1985) is based on the five-factor model and measures not only the five domains, but also six traits (facets or features) that define each domain. It measures impulsivity as a factor of the neuroticism scale. It has been used and validated in clinical populations including autism (Hesselmark et al., 2015).

Dickman's Functional and Dysfunctional Impulsivity Inventory (DII). The 23 question Dickman's functional and dysfunctional impulsivity inventory (DII; Dickman, 1990) is a well-known measure of both the positive and negative aspects of impulsivity. Consequently, it measures two factors of impulsivity, functional and dysfunctional, with 12 questions focused on dysfunctional impulsivity (DI scale; Di Milia, 2013; Whiteside & Lynam, 2001). Di Millia

(2013) developed a revised nine question DI scale that distinguishes high and low dysfunctional impulsivity normed against a wider population than the original version.

Behavioral Inhibition/Behavioral Activation Scales (BIS/BAS). The 24-question behavioral inhibition scale and behavioral activation scale (BIS/BAS, Carver & White, 1994) is based on Gray's theory of brain functions and behavior. It assumes two orthogonal neurobiological correlates and systems (Carver & White, 1994). The first, the behavioral inhibition system (BIS), regulates aversive motivation and is comparable to behavioral response inhibition (Carver & White, 1994). The second, the behavioral activation system (BAS), regulates appetite motivation (Carver & White, 1994). The BAS scale comprises 13 questions and is most comparable to impulsivity, measuring three factors: reward responsiveness, fun seeking, and drive (Carver & White, 1994).

Barkley Deficits in Executive Functioning, Self-Restraint/Inhibition Scale (BDEFS). Barkley (2011), the originator of a theoretical framework for behavioral response inhibition used in this study, developed a 19-question subdomain of the Barkley deficits in executive functioning, self-restraining/inhibition scale (BDEFS). The instrument measures a single factor, self-restraint/inhibition. It has been used in clinical settings, including for ADHD (Kamradt et al., 2014).

Sensation Seeking Scale (SSS-V). The 40-question sensation seeking scale (SSS-V; Zuckerman, 1994) uses forced choice answers. It measures four factors including disinhibition and has been used in multiple clinical settings, including ADHD (Ballon et al., 2015). An eight-question brief sensation seeking scale (BSSS; Hoyle et al., 2002) focuses on the sensation seeking factor, a facet of cognitive impulsivity.

EASI-III Impulsivity Scales. The 20-question EASI-III impulsivity scales (Buss & Plomin, 1975) are among the oldest measures of impulsivity. They are focused on the four-temperament theory of personality. The questions cover the four subscales of impulsivity in the broader instrument: inhibitory control, decision time, sensation seeking, and persistence.

Impulsive Compulsive Behaviors Checklist (ICBC). The impulsive 33-question compulsive behaviors checklist (ICBC; Guo et al., 2017) is a relatively recent measure that focuses on both impulsivity and compulsivity. As discussed previously, impulsivity and compulsivity often co-occur and merge at deficits in behavioral response inhibition. Each is a distinctly measured factor and the instrument is useful in clinical settings both within an inter-disorder impulsivity-compulsivity dyad where there is cycling between their extremes and an intra-disorder impulsivity-compulsivity dyad for comorbid disorders. Although, due to its relatively recency, it has not been widely adopted, it has been validated against a community sample (Guo et al., 2017). Its measure of trait impulsivity compares favorably to the UPPS-P and UPPS-R (Guo et al., 2017).

Other Trait Self-Report Measures of Impulsivity. There are a number of additional self-report neuropsychological measures of impulsivity in the literature including the following 10 instruments: the 53 question lifetime history of impulsive behaviors (LHIB-Q53, Coccaro & Schmidt-Kaplan, 2012), which measures impulsivity longitudinally; the 17 question recent rash impulsivity scale (RRIS), which measures impulsivity over brief periods and its timescale removed 17 question trait rash impulsivity scale (TRIS; Mayhew & Powell, 2014); the 24 question multidimensional personality questionnaire control scale (MPQ; Tellegen, 1985), the 16 question subscale personality research form impulsivity scale of the personality research form (PRF; Jackson, 1984), the 14 question the positive urgency measure (PUM; Cyders et al., 2007),

the 38 question risky, impulsive and self-destructive behavior questionnaire (RISQ; Sadeh & Baskin-Sommers, 2016); the 48 question sensitivity to punishment and sensitivity to reward questionnaire (SPSRQ; Torrubia et al., 2001), and the eight question temperament and character inventory impulsiveness (TCI; Cloninger et al., 1991) subscale of the novelty seeking dimension and its nine question subscale from the revised novelty seeking dimension (TCI-R; Cloninger, 1999).

Behavioral State Measures. Below are brief descriptions of laboratory behavioral (neuropsychological) measures of impulsivity and BRI, including one or more BRI facets (prepotent response inhibition, prepotent response extinction, interference control). The measures discussed are those that most often appear in the research literature related to impulsivity and BRI endophenotypes and their role in the behavioral phenotypes discussed in this chapter (i.e., ADHD, ASD, schizophrenia, and BPD). There are a number of other measures not discussed below. Those that were used in this study (go/no-go task, stop-signal task, and WCST) are discussed in greater detail in Chapter 3. Variants of those selected measures not used in this study are discussed below, and not in Chapter 3. As previously discussed, measures used in this study were selected based on their ability to discriminate two related facets (factors, features, or components) of BRI, namely prepotent response inhibition and prepotent response extinction, to the exclusion of interference control, which is based on distinct neural network circuitry and implicates cognitive impulsivity. For example, the Stroop test, Simon task, flanker task, and antisaccade task discussed below all combine measures of interference control with measures of prepotent response inhibition and/or prepotent response extinction. Each behavioral measure described below can serve as an endophenotype, and the scales and subscales of each measure

can also serve as endophenotypes (i.e., decomposed endophenotypes that can comprise deep endophenotypes).

Go/No-Go Task (GNG). The go/no-go (GNG) task (Newman et al., 1985) is discussed in detail in Chapter 3. It is arguably the most widely used laboratory behavioral measure (RDoC paradigm) of impulsivity and BRI (Wu et al., 2023; Xia et al., 2020). The GNG measures the ability to inhibit a habitual prepotent response (action restraint) in the presence of a rare stop stimulus (Wu et al. 2023; Xia et al., 2020). Failure to properly inhibit a prepotent go response in response to the presence of a stop stimulus is indexed by the *commission errors* (CE; proportion of failed no go responses) outcome variable of the instrument (Schachar et al., 2011; Wright et al., 2014). The GNG, and its measures, can serve as putative endophenotypes for DSM psychiatric disorders as it is as much as 45% heritable (Schachar et al., 2011). Variants of the GNG include the go/no-go association task (GNAT; Nosek & Banaji, 2001).

Stop-Signal Task (SST). The stop-signal task (SST; Lappin et al., 1966; Logan et al., 1997) is discussed in detail in Chapter 3. It is one of the most widely used laboratory behavioral measures (paradigms) of impulsivity and BRI and is often confounded or considered interchangeable with the GNG, which, as discussed elsewhere in this chapter, it is not (Senkowski et al., 2023; Raud et al., 2020). Like with the GNG, the SST measures inhibition of a prepotent response. However, unlike the GNG, where a habitual prepotent action must be inhibited prior to action initiation, with the SST, the prepotent habitual action must be inhibited after it has already been initiated (action cancellation or extinction; Schachar et al., 2011; Senkowski et al., 2023). Consequently, with the GNG, a prepotent response must be inhibited, and with the SST, a prepotent response already begun must be extinguished. For this reason, action cancellation (measured by the SST) is termed in this study as prepotent response

extinction, to capture the fact that both measures deal with primed prepotent habitual actions. Other terms for the output of the SST in the literature, which corresponds to Barkley's second facet of BRI, do not capture this common theme. In essence, the SST uses a horse race model between completion of the action and cancelation of the action—that is, between response execution and response extinction (Schachar et al., 2011). The stop signal reaction time (SSRT) is a key outcome variable in the SST that measures the temporal latency of time between the stop signal and its extinction (Congdon et al., 2012; Schachar et al., 2011; Senkowski et al., 2023; Thunberg et al., 2024). While there are few studies investigating the heritability of SST measures (and, by proxy, prepotent response extinction), it has been shown to have significant heritability (as high as 48% SSRT heritability) and thus has also been considered a putative endophenotype for psychiatric disorders (Schachar et al., 2011; Thunberg et al., 2024). The SSRT outcome variable of the SST has been used to differentiate BRI in psychiatric disorders, including ADHD, schizophrenia, and ASD (Lyszyk & Schachar, 2010).

Wisconsin Card Sorting Test (WCST). The Wisconsin Card Sorting Test (WCST; Berg, 1948) is a neuropsychological laboratory behavioral measure (paradigm) of set-shifting and cognitive flexibility (Berg, 1948; Monchi et al., 2001). It is discussed in detail in Chapter 3. The WCST is also used to test, and serves as a proxy for, neurobiological function of the prefrontal cortex (PFC), particularly the dorsolateral prefrontal cortex (dlPFC), and related executive functions, as confirmed using various neuroimaging methods, including DTI and fMRI (Lombardi et al., 1999; Monchi et al., 2001). In particular, a high number of perseverative responses (PR) on the WCST are characteristic of dlPFC damage (Lombardi et al., 1999; Monchi et al., 2001). High perseverative responses (PR) on the WCST also represent a proxy for dysfunction of the caudate nucleus (CN) in the frontostriatal region of the basal ganglia

(Lombardi et al., 1999; Monchi et al., 2001). CN dysfunction has implicated impulsivity in ADHD, ASD, schizophrenia, Huntington's disease and Parkinson's disease (including via use of the WCST), implicating, among others, executive function precursive D2/D3 dopamine receptors (Dalley et al., 2011; Driscoll et al., 2022; Eldridge et al., 2023; Gorora et al., 2024; Lee et al., 2009; Tong et al., 2024). The relationship between the dlPFC and CN as well as the literature regarding CN dysfunction in the above diseases and disorders implicates choice impulsivity in particular (Antonelli et al., 2014; Martinez et al., 2020). However, in light of the literature cited previously in this chapter regarding motor impulsivity, dysfunction of projections from the CN to the dlPFC (i.e., bypass of the mesocortical dopaminergic neural networks in favor of mesolimbic projections) then implicates motor impulsivity. Using PET and SPECT neuroimaging (see later in this chapter for description of these methods) a decrease in CN and ventral striatal dopamine transporter (DAT) tone has implicated the BIS-11 motor impulsivity subscale (Smith et al., 2018). Further, CN striatal dopamine has been implicated in both the GNG and SST (Dalley et al., 2011). Consequently, when the WCST is used in studies with the BIS-11 self-report psychometric measure and GNG and SST laboratory behavioral measures (paradigms), as was the case in this study, it can help discriminate cognitive (choice) and motor impulsivity when one, but not the other is present, but not necessarily when both are present as part of the broader construct of impulsivity. Further, the WCST serves as a proxy neurobiological (neuroimaging) measure when a study, such as this study, does not use neuroimaging.

Conners Continuous Performance Test (CCPT). The Conners continuous performance test (CCPT), based on earlier continuous performance tests (CPTs; Beck et al., 1956), is a measure of executive attention and inhibition (Connors, 2000). The test is somewhat similar to the GNG in that subjects are required to inhibit prepotent responses (pressing a key on a

keyboard) during the 10% of trials of when an X appears instead of any other random letter (Homack & Riccio, 2006; Soreni et al., 2009). While the current version is the CCPT-3 (Conners, 2014), the CCPT-2 remains the most widely used (Homack & Riccio, 2006; Shaked et al., 2020). Outcome measures of impulsivity of the CCPT-2 include commission errors, preservative responses, and anticipatory responses (Shaked et al., 2020). Consequently, these outcome measures should positively correlate with commissions errors of the GNG and SSRT of the SST as well as outcome measures of the Stroop Test (discussed next; Shaked et al., 2020). The CCPT and CCPT-2 are among the most widely used instruments in the diagnosis of ADHD because it measures both attention (via the ability to continue to focus on a stream of letters looking for the rare 'x') and impulsivity (via the ability to inhibit prepotency from pressing the button when the 'x' appears; Homack & Riccio, 2006; Shaked et al., 2020; Soreni et al., 2009). The CCPT has strong internal consistency and high test-retest reliability of around .78 (Shaked et al., 2020; Soreni et al., 2009). However, as with other laboratory behavioral measures, the CCPT-2 poorly correlates with self-report measures (Shaked et al., 2020).

Stroop Test. The Stroop test (Stroop, 1935) measures interference control by asking a subject to read a word describing a color while the color of the font for the word is different or the same thereby measuring the difference between response times (via outcome variable of mean reaction time [mRt]) to name the color of the word and to measure commission errors as a proxy for conflict monitoring (Macleod, 1991). Typically, a subject is slower to respond when the color of the word and its description conflict, resulting in the so-called Stroop effect (Macleod, 1991; Roelofs, 2021). As a proxy for neurobiological correlates, neuroimaging studies indicate that the Stroop test implicates the ACC and dlPFC for interference control conflict resolution (cognitive control; Milham et al., 2003; Pardo et al., 1990). Recently, it has been

suggested that the Stroop effect is due to response competition (racehorse conflict) rather than response exclusion (Roelofs, 2021). In that respect, to the extent it can serve as a measure of inhibition (inhibiting the primed prepotent word association in favor of the correct color association) it is a closer proxy of inhibition to the SST (the racehorse model) rather than the GNG.

Simon Task. The Simon task (Simon & Wolf, 1963) is a test of choice reaction (another conflict resolution test) and interference control, whereby subjects are asked, for example, to press a button on the right when a red object appears and a button on the left when a green object appears while ignoring temporal changes in the locations of the objects relative to location of the buttons (Proctor, 2011). Typically, responses are faster (as measured by mean reaction time [mRT]) and more accurate (as measured by commission errors) when the relative position of the stimulus is congruent with the location of the button resulting via the so-called Simon effect (Proctor, 2011). Variations of the Simon task have incorporated other sensory stimuli expanding the Simon effect beyond visuospatial dimensions (Proctor, 2011). Like the Stroop test, the Simon task combines interference control with response conflict inhibition in a racehorse model. Thus, like the SST, prepotent response extinction is in the form of a race between the correct response and the latent primed prepotent response tied to the location of the stimulus and button (Proctor, 2011). Also like the Stroop test, neuroimaging studies have indicated that the ACC and dlPFC are implicated in the Simon task under the domain of cognitive control (Wang & Weekes, 2014).

Flanker Task. The flanker task (Eriksen & Eriksen, 1974), is another measure of interference control, choice conflict resolution, and response inhibition. While the original iteration of the flanker task used letters, current embodiments use arrows for a target whereby subjects are asked to tap directional buttons while the target was flanked with congruent or

incongruent directional distractors (Kopp et al., 1996; Ridderinkhof et al., 2021). Choice reaction times (RT) differ when congruent flankers are present versus incongruent flankers (Kopp et al., 1996; Ridderinkhof et al., 2021). Neurobiologically, the ACC is more activated during performance of the flanker task in the presence of incongruent flankers versus congruent flankers (Davelaar, 2013). Both the N200 and P300 ERP components (discussed later in this chapter) have been implicated by the flanker task (Kopp et al., 1996; Ridderinkhof et al., 2021). As with other tasks and tests that contain a BRI measure, the flanker task has been used in the study of both neurological and behavioral disorders such as Parkinson's disease and ADHD (Ridderinkhof et al., 2021).

Antisaccade Task. Like the WCST, the antisaccade task (Hallett, 1978) is used as a proxy for PFC neurobiological function and dysfunction (Everling & Fischer, 1998). It is another measure of interference control, choice conflict resolution, and prepotent response inhibition (Hutton & Ettinger, 2006). It is based on saccadic eye movements, which comprise short bursts of directional movement, rather than smooth movement along a temporal and directional continuum (Everling & Fischer, 1998). Stimuli incite saccadic movements towards the stimulus, so the ability to inhibit a saccadic response in the direction of an interfering stimulus or the ability to inhibit a saccadic reflex in the opposite direction of a target stimulus characterizes the antisaccade (Everling & Fischer, 1998). In the antisaccade task, a subject has to maintain focus on a central fixation point and must inhibit a saccadic reaction to an interfering stimulus along the periphery and then generate a saccade in the opposite direction of the interfering stimulus (antisaccade; Everling & Fischer, 1998). The dlPFC is the primary neurobiological correlate of the antisaccade task based on neuroimaging studies, including fMRI, EEG/ERP and EEG/MEG (methods discussed later in this chapter; Hutton & Ettinger, 2006; Waldthaler et al., 2022). The

antisaccade task has been used in research relating to numerous behavioral and neurological disorders including ADHD, autism, schizophrenia, and Parkinson's disease (Coors et al., 2023; Everling & Fischer, 1998; Hutton & Ettinger, 2006; Sahuquillo-Leal et al., 2024; Sherigar et al., 2022; Waldthaler et al., 2022; Zhu et al., 2024).

Choice Impulsivity Measures Commonly used with BRI Measures. As discussed previously, delay discounting—the tendency to discount delayed rewards in favor of more immediate rewards—is a facet of choice impulsivity under cognitive impulsivity (discussed below; Matta et al., 2012; Odum, 2011). The delay discounting task is the primary measure of choice impulsivity (Belles et al., 2023; Cherek et al., 1997; Frye et al., 2016; Matta et al., 2012). Numerous delay discounting tasks can be used in conjunction with BRI measures (Cherek et al., 1997; Frye et al., 2016; Matta et al., 2012). For example, the delay discounting task is often combined with one or more of the above measures of BRI in RDoC studies to study correlations in dopaminergic system function between impulsive choice (choice impulsivity) and impulsive action (motor impulsivity; Belles et al., 2023). Choice impulsivity and motor impulsivity are thought to co-occur in numerous DSM disorders, including ADHD and BPD (Belles et al., 2023).

The Iowa gambling task (IGT; Bechara et al., 1994) is a measure of choice impulsivity. Like the WCST, it can serve as a proxy for PFC function and dysfunction, particularly the dlPFC, orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC), but also the ACC, as measured by fMRI (Li et al., 2010). It has been used in the study of numerous neurological and behavioral disorders, including schizophrenia, ADHD, and Parkinson's disease (Beulow & Suhr, 2009; Evens et al., 2016; Li et al., 2010; Spencer & Anderton, 2024; Zeif & Yechiam, 2020). Numerous studies have used the IGT to help discriminate deficits in choice

impulsivity versus motor impulsivity in various behavioral and neurological disorders. For example, a meta-analysis of the IGT with Autism indicated that there is no difference between Autistic individuals and controls on IGT performance (Zeif & Yechiam, 2020). In contrast, a meta-analysis of the IGT with Parkinson's disease indicated impaired IGT performance in Parkinson's patients versus controls (Evens et al., 2016). Similarly, schizophrenic patients have shown impairment on the IGT, but not WCST in some studies, while also showing WCST impairment in others (Beulow & Suhr, 2009). IGT studies in ADHD patients have also shown mixed results (Beulow & Suhr, 2009). Contrary to historical lack of correlation between self-report and laboratory behavioral measures, IGT performance in ADHD patients have positively correlated with BIS-11 and the CCPT-II, but other studies have shown more contradictory results (Beulow & Suhr, 2009; Mallow-Dinz et al., 2007).

Table 2

Major Laboratory Behavioral Measures Related to BRI

Measure	BRI Facet	Primary Outcome Measure	Neural Correlates	Herit.	Clinical Use
Go/No-Go Task (GNG)	Prepotent Response Inhibition (Action Restraint)	Commission Errors (Failed No-Go)	dlPFC, rIFC	45% ^a	ADHD, ASD, Schizophrenia
Stop-Signal Task (SST)	Prepotent Response Extinction (Action Cancellation)	Stop Signal Reaction Time (SSRT)	pre-SMA, IFG	48% ^a	ADHD, ASD, Schizophrenia
Wisconsin Card Sorting Test (WCST)	Interference Control (Set-shifting)	Perseverative Errors	dlPFC, Caudate Nucleus (CN)	NR	ADHD, Schizophrenia, Parkinson's, Huntington's

Measure	BRI Facet	Primary Outcome Measure	Neural Correlates	Herit.	Clinical Use
Conners CPT (CCPT-2)	Prepotent Response Inhibition	Commission Errors, Preservative Responses	dIPFC, ACC	Test-retest: 0.78 ^b	ADHD (Primary)
Stroop Test	Interference Control (Conflict Resolution)	Mean Reaction Time (mRT), Commission Errors	ACC, dIPFC	NR	ADHD, Various Disorders
Simon Task	Interference Control (Conflict Resolution)	Mean Reaction Time (mRT), Commission Errors	ACC, dIPFC	NR	Various Disorders
Flanker Task	Interference Control (Conflict Resolution)	Reaction Time (RT) Differences	ACC	NR	ADHD, Parkinson's
Antisaccade Task	Prepotent Response Inhibition	Saccadic Error Rate	dIPFC	NR	ADHD, Autism, Schizophrenia, Parkinson's
Delay Discounting Task	Choice Impulsivity (Delay Discounting)	Discounting Rate (k parameter)	OFC, vmPFC	NR	ADHD, BPD
Iowa Gambling Task (IGT)	Choice Impulsivity (Decision Making)	Net Score (Advantageous Choices)	dIPFC, OFC, vmPFC, ACC	NR	ADHD, Schizophrenia, Parkinson's

Note: BRI = Behavioral Response Inhibition; dIPFC = dorsolateral prefrontal cortex; rIFC = right inferior frontal cortex; pre-SMA = pre-supplementary motor area; IFG = inferior frontal gyrus; ACC = anterior cingulate cortex; OFC = orbitofrontal cortex; vmPFC = ventromedial prefrontal cortex. NR = not reported. Herit. = heritability.

^a (Schachar et al., 2011). ^b (Shaked et al., 2020).

Impulsivity Types, Sub-Constructs, Facets, Features, Components, Factors, Levels, and Variables

As described in the beginning of this section, impulsivity has numerous definitions in the literature. Many such definitions are distinct and orthogonal to each other (Cyders, 2015). Such definitions often describe impulsivity as a trait or state. Other definitions characterize impulsivity in terms of choice, attention, non-planning, cognition, or motor action. Each of these distinctions can be described as a type, sub-construct, facet, feature, component, factor, level, or variable of the broad construct of impulsivity. Each can also be considered constructs in their own right, with sub-types, facets, features, components factors of variables of their own or of each other. Thus, each can be considered endophenotypes that comprise a deep endophenotype. Each of these is briefly discussed below as separate constructs or sub-constructs in the literature and summarized in Figure 4.

Trait Impulsivity. Trait impulsivity, also called impulsive personality, is a latent longitudinally and temporally stable and consistent highly heritable personality trait (Beauchaine et al., 2017; Buhler et al., 2023). It marks a facet of temperament that predicts one's reactions to day-to-day perturbations to one's environment (Buhler et al., 2023). It is characterized by behavior without forethought, lack of self-control, a preference for immediate gratification, and poor planning (Beauchaine et al., 2017). Like with impulsivity generally, however, trait impulsivity can be segregated into different components. For example, Rogers et al. (2021) studied trait impulsivity (impulsive personality) with latent analysis in 599 participants using the S-UPPS-P and parsed trait impulsivity into high urgency, high sensation seeking, and low lack of perseverance and premeditation (i.e., dysfunctional behavioral response inhibition).

In part due to trait impulsivity's temporal stability, many studies have focused on the heritable neurobiological correlates of trait impulsivity, including the mesocorticolimbic dopamine systems (Beauchaine et al., 2017). Still others focus neurogenetic correlates of trait impulsivity (Beauchaine et al., 2017). While DSM externalizing disorders are highly polygenic, certain neurogenetic correlates of impulsivity merge across them, including polymorphisms (alleles) of genes that code for dopamine receptors DRD2, DRD4 and DRD5, dopamine transporter (DAT1), monoamine oxidase A (MAOA), and catechol-O-methyltransferase (COMT; Gizer et al., 2016; Spencer & Anderton, 2024). For example, Buhler et al. (2023) studied a sample of 905 participants segregated by the BIS-11 and identified three candidate gene SNPs (alleles) implicated in catecholaminergic neurotransmitter pathways: DRD2/ANKK Taq1A, DRD2 C957T, and COMT Val158Met allelic genotypes.

While trait impulsivity has been most often associated with self-report measures, its link with behavioral response inhibition has also implicated laboratory behavioral measures. For example, Aichert et al. (2012) studied the relationship between trait impulsivity and prepotent response inhibition. As described previously and below, prepotent response inhibition is the first facet of behavioral response inhibition under Barkley's Theory of Inhibitory Deficits. The authors studied a sample of 504 neurotypical participants using the BIS-11 self-report measure and four putative laboratory behavioral measures of prepotent response inhibition, the go/no-go task, stop-signal task, antisaccade task, and Stroop task (Aichert et al., 2012). Based on cross loadings of these tasks, the authors concluded that BIS-11 impulsivity explained a relatively low 12% of the variance of prepotent response inhibition.

While generally consistent with the low correlation between self-report and laboratory behavioral measures in the literature, it is possible that Aichert et al. (2021), and the literature they cited, conflate the facets of trait impulsivity measured by the BIS-11 and behavioral response inhibition measured by the laboratory behavioral measures. As mentioned previously, the BIS-11 measures three higher order and six lower order factors of impulsivity and the laboratory behavioral measures each measure numerous factors. If these measures are dimensionalized and decomposed into their factors, facets, components, and features and each of those compared, it may be possible to identify stronger relationships between these decomposed factors and between self-report measures of trait impulsivity and laboratory behavioral measures of behavioral response inhibition or state impulsivity. This is a similar approach to that which this study took.

State Impulsivity. State impulsivity, also called behavioral impulsivity, is an ephemeral phase transition towards a dysregulated response to an internal or external stimulus, including through behavioral disinhibition (Buhler et al., 2023; Dewi et al., 2023). As with trait impulsivity, state impulsivity is multifaceted and has been parsed into various facets including impulsive decision making, impulsive response initiation, and behavioral disinhibition (Nguyen et al., 2018). Also, as with trait impulsivity, state impulsivity has been the focus of various studies to identify its neurobiological and neurogenetic correlates. Many such studies identify orthogonal relationships among facets based in their neurobiological and neurogenetic liability, for example, discriminating neural correlates of prepotent response inhibition (behavioral disinhibition) and impulsive decision making (Bari & Robbins, 2013; Meda et al., 2009).

Where trait impulsivity is the focus of self-report measures, state impulsivity is the focus of laboratory behavioral measures (Muele, 2013; Nguyen et al, 2018). Again, however, deficits in BRI lead to state impulsivity and, consequently, measures of state impulsivity are arguably measures of deficits in BRI. Sasinka et al. (2021), for example, developed a behavioral measure based on the go/no-go task to measure behavioral impulsivity, that is, the prepotent response inhibition facet of behavioral response inhibition. The authors compared their go/no-go behavioral measure to self-report UPPS-P and S-UPPS-P to determine its correlation with trait impulsivity by identifying facets of the self-report measures that covary with facets of the behavioral measure, a somewhat similar decomposition concept to that used in this study, although their study demonstrated weak associations.

If trait impulsivity can be characterized as a global tendency to be impulsive, as a lifelong temperament that favors impulsive action, state impulsivity can be characterized as a dynamical local sensitivity to impulsive action (see van Baal et al., 2022). In other words, one's tendency to be impulsive may be regulated by one's temporal in-the-moment sensitivity to transition from a base level of inhibition to partial or complete disinhibition. It can be measured either as a discrete phase transition from an inhibited to a disinhibited state or as a continuous phase transition from inhibition to increasing disinhibition. This latter aspect is one of magnitude of disinhibition or magnitude, intensity, or severity of impulsivity (van Baal et al., 2022). Put another way, the concept that impulsivity symptom intensity can be a product of sensitivity to triggers is similar to the concept put forth by Miskewicz et al. (2022) for borderline personality disorder (BPD) that stable personality traits (e.g., trait impulsivity) predict the perception of trigger intensity, which, in turn, predict symptom intensity (e.g., state impulsivity). Applying the above concept to BPD, it would suggest that the thin-skinned over sensitivity (constitutional

hypersensitivity) of BPD patients to triggers, regardless of actual trigger intensity, drives the severity of impulsive behaviors in this case, rather than the actual intensity of the trigger itself. Alternatively, high trigger intensity coupled with high trigger sensitivity can compound symptom intensity, here state impulsivity.

Previously, it was noted that BPD patients have higher impulsivity levels than even ADHD patients, which have higher levels than in other disorders. The discussions in this chapter of the types, sub-constructs, factors, and components of impulsivity, coupled with the presence of trait and state impulsivity, in light of sensitivity to activation, begin to suggest that the symptom intensity in BPD, ADHD, ASD, and schizophrenia may be explained by the compounding presence of various types (and facets and factors) of impulsivity in these patients (behavioral phenotypes). For example, a patient with one of these disorders may have both high levels of trait impulsivity and state impulsivity (or high levels of selected factors or facets of each), and high levels of choice impulsivity, motor impulsivity, cognitive impulsivity (see next section), attentional impulsivity, and/or non-planning impulsivity. However, as previously suggested and the focus of this study, motor impulsivity due to deficits in BRI is arguably the operational symptomatic embodiment of other forms of impulsivity. In other words, perhaps other forms of impulsivity can upregulate the frequency or intensity of motor impulsivity (a form of state impulsivity or behavioral impulsivity) or both. Pathological motor impulsivity (impulsive action) thus can be described as the observable pathological maladaptive externalized or internalized action, or reaction to a trigger or stimulus, that elicits a negative endogenous or exogenous environmental reaction or consequence and is optimally measured by the BIS-11 self-report measure of trait impulsivity and the go/no-go and stop signal tasks of state impulsivity (Chowdhury et al., 2017; Dewi et al., 2023).

State impulsivity can also be characterized in the context of its temporal durability, a measure of intensity of its stickiness. Combined with the above discussion, this suggests that state impulsivity is more dynamic than trait impulsivity, which is relatively stable over time, a somewhat obvious conclusion from its definition and operationalized facets. State impulsivity applies to the here and now and is more sensitive to environmental conditions in the moment, while trait impulsivity is more innate, focusing on stable traits comprising impulsivity (Barnhart & Beulow, 2017). State impulsivity thus implicates behavioral response inhibition, which implicates self-control, itself a facet of self-regulation and cognitive control (Nigg, 2017). Whether state impulsivity or trait impulsivity drives disinhibition, rather than just implicates it, however, is a different discussion entirely and is still in dispute (Nigg, 2017; van Baal et al., 2022).

Cognitive Impulsivity. Cognitive impulsivity is often defined in the context of delay discounting as is the case with choice impulsivity (choice impulsivity is described in the next section; Curtis et al., 2018). Cognitive impulsivity can be defined as one's myopic inability to properly balance the pros and cons of immediate versus future choices (Arce & Sansisteban, 2006). It can also be considered a broader parental sub-construct of both non-planning and attentional impulsivity, which are discussed below (Arce & Sansisteban, 2006). Each of attentional and non-planning impulsivity, as traits, can be measured by two BIS-11 factors and cognitive impulsivity generally can be measured behaviorally by the Iowa Gambling Task (as can choice impulsivity; Arce & Sansisteban, 2006; Barreno et al., 2019). In that sense, while cognitive impulsivity is a narrower construct than impulsivity, it is broader than choice, attentional, and non-planning impulsivity, each of which can be argued to be facets of cognitive impulsivity (Barreno et al., 2019). Consequently, studies of cognitive impulsivity may suffer

from the same limitations as studies of the broad construct of impulsivity in that cognitive impulsivity is a multidimensional sub-construct of impulsivity (Barreno et al., 2019).

There are studies of cognitive impulsivity as a sub-construct in the literature, including those that focus on its neurobiological correlates. For example, Chiang et al. (2015) studied cognitive impulsivity in 50 ADHD patients and 50 controls. Chiang et al. (2015) used structural MRI to measure white matter density in a sample that had been segregated into testing groups using the Conners continuance performance test (CCPT). CCPT scales have been linked to candidate genes for impulsivity, including the DRD4-7R polymorphism (Chiang et al., 2015). Chiang et al. (2015) observed that the clinical sample had differential white matter when compared to controls. However, while purporting to measure cognitive impulsivity, the CCPT is actually a measure of attentional performance and thus attentional impulsivity (Chiang et al., 2015). Therefore, arguably, the CCPT measures a facet of cognitive impulsivity rather than cognitive impulsivity itself (Chiang et al., 2015). Consequently, it may be better to discuss the literature of cognitive impulsivity in the context of its sub-constructs of choice, attentional, and non-planning impulsivity. Each of these sub-constructs is discussed below.

Choice Impulsivity. Choice impulsivity (impulsive choice) is a preference for immediate smaller rewards (immediate gratification) over larger delayed rewards (Bernosky-Smith, 2018; Hamilton et al., 2016; Fineberg et al., 2014; Jung & Kim, 2023; Kim & Im, 2019) or “a choice for small-immediate reinforcers over larger-delayed reinforcers” (Patros et al., 2016, p. 163). It is often characterized as a type of behavioral impulsivity (Kim & Im, 2019). Such a distinction may or may not be a proper categorization in light of unique neurobiological correlates between cognitive processes and behavioral (motor) processes as discussed previously and below. Several facets of choice impulsivity have been described in the literature, including lack of planning,

disregard of future consequences, delay discounting, and temporal discounting (Gelino et al., 2024; Hamilton et al., 2016; Jung & Kim, 2023; Moro et al., 2023). As noted previously, these factors are often included as factors of the broader construct of impulsivity or its sub-construct, cognitive impulsivity. Based on the component where the delay discounts the larger reward, choice impulsivity is also referred to as delay-discounting impulsivity (Gelino et al., 2024; Hamilton et al., 2016; Jung & Kim, 2023) or reward-delay impulsivity (Jung & Kim, 2023; Patros et al., 2016).

Choice impulsivity is also often referred to as a more specific symptom of psychopathology. It has been observed to be more elevated in patients with ADHD, substance use disorders, bipolar disorder, and borderline personality disorder (Chan et al., 2023; Fineberg et al., 2014; Hamilton et al., 2016; Jung & Kim, 2023; Patros et al., 2016; Wang et al., 2020). Choice impulsivity is poorly correlated with motor impulsivity (rapid response impulsivity, discussed below) and even orthogonal to it (Hamilton et al., 2015; Wang et al., 2016). Its measures are similarly distinct from those for motor impulsivity (Wang et al., 2016). Measures of choice impulsivity are typically laboratory behavioral measures focused on temporal discounting, such as the delay-discounting task (DDT) and experimental discounting task (EDT; Chamberlain & Fineberg, 2015; Fineberg et al., 2014; Gelino et al., 2024; Moro et al., 2023; Wang et al., 2016).

From a neurobiological standpoint, choice impulsivity implicates reward related areas of the brain and their neural circuit connections in and between the ventral striatum (VS), medial prefrontal cortex (mPFC), anterior dorsolateral prefrontal cortex (dlPFC), ventrolateral and ventromedial prefrontal cortex (vlPFC/vmPFC), orbitofrontal cortex (OFC), medial rostral prefrontal cortex, anterior cingulate cortex (ACC), and hippocampus (Fineberg et al., 2014;

Hamilton et al., 2016; Jung & Kim, 2023; Moro et al., 2023; Wang et al., 2016). These are distinct neural circuits from those implicated in rapid-response impulsivity (motor impulsivity) discussed next (Chamberlain & Fineberg, 2015; Fineberg et al., 2014; Hamilton et al., 2016; Wang et al., 2016). Wang et al. (2020) for example studied a sample of 429 participants using resting-state functional magnetic resonance imaging (rsfMRI; the neurophysiological measure) while participants performed a version of the DDT (the behavioral measure). The authors determined that delay-discounting related to circuits comprising projections between the nucleus accumbens (NA; part of the striatum in the basal ganglia), limbic system (including the hippocampus and amygdala), caudate nucleus (also part of the striatum), and dorsomedial prefrontal cortex.

Attentional Impulsivity. Attentional impulsivity is one of the three factors of trait impulsivity measured by the BIS-11 (Patton et al., 1995) and arguably a component of cognitive impulsivity. It is often described as a deficit in one's ability to focus or concentrate (Cservenka & Ray, 2016; Meule, 2013; Zare et al., 2023). Unsurprisingly, it is often associated with ADHD and is often a target of studies to understand both neuropsychological and neurobiological correlates of ADHD (Zare et al., 2023). For example, Dang et al. (2016) used the BIS-11 and a behavioral measure of attention (the Test of Variables of Attention [TOVA]) to study a sample of 71 neurotypical adults with structural MRI to assess the BIS-11 factors in the context of ADHD from an RDoC dimensional perspective.

Contrary to most studies in the literature, Dang et al. (2016) selected subscale measures of both a trait measure (the BIS-11) and a behavioral measure (the TOVA) to attempt to better discriminate neuroimaging measures (structural MRI) to then better characterize neurobiological correlates comprising asymmetric caudate nucleus volume. This is a similar approach to that

taken by this study. The authors felt that by better discriminating the relationship between a self-report measure and a behavioral measure of impulsivity, they can better differentiate their neurobiological correlates. This is an example of decomposing facets of impulsivity across measures of trait and state impulsivity as was the case with this study. The authors determined that asymmetry in caudate nucleus volume differentially predicted both trait self-report attentional impulsivity and a behavioral attentional measure for ADHD dimensionally in a normal population (Dang et al., 2016). This is also an example of a transdiagnostic RDoC perspective, rather than a categorical DSM perspective. Further, Dang et al. (2016) concluded that caudate asymmetry only correlated with attentional impulsivity subscale of the BIS-11 and not with motor impulsivity or non-planning impulsivity. This further demonstrates the benefit of a decomposed dimensional approach similar to this study, which can thus be applied beyond a given mental disorder, such as ADHD.

Non-Planning Impulsivity. Non-planning impulsivity can be defined as a cognitive focus on the moment without reference to the future (Lage et al., 2012). The literature on non-planning impulsivity as a sub-construct is scant. Often it is reported in the context as a sub-scale of the BIS-11 (Celik et al., 2023; Lage et al., 2012; Zare et al., 2023). It is also often considered an analog rather than a sub-construct of cognitive impulsivity (Lage et al., 2012). Interestingly, some studies have suggested that non-planning impulsivity is the most stable factor of the BIS-11 and that attentional impulsivity is the least stable factor (Lau et al., 2022).

In the context of neurobiological correlates, Reeves et al. (2012) sought to decompose and segregate the factors of the BIS-11 in light of prior research that treated impulsivity as a unitary construct. Reeves et al. (2012) studied the association between BIS-11 factors and D2/D3 dopamine receptor availability in the ventral striatum. While associations have been previously

identified in the literature based on impulsivity as a broad construct, they were often dependent on the behavioral (neuropsychological) measure used (Reeves et al., 2012). This suggested that associations were specific to distinct facets of impulsivity rather than the broad impulsivity construct itself (Reeves et al., 2012). Reeves et al. (2012) used positron emission topography (PET) neuroimaging in 23 neurotypical participants. These authors identified a significant association between non-planning impulsivity and D2/D3 availability, but not other factors. This is an example of an increasing trend in the literature suggesting that individual facets (sub-constructs or factors) of impulsivity implicate unique neurobiological and neuropsychological correlates, including distinct neural network circuits.

Although few studies have done so, in light of unique neurobiological associations, non-planning impulsivity has been considered as a potential candidate endophenotype (as opposed to the broader construct of impulsivity), including in candidate genes studies using various neuropsychological measures. For example, Lage et al. (2012) studied the association between the candidate gene 5-HTTLPR (serotonin-transporter-linked promoter region) and both self-report subscales of the BIS-11 (i.e., impulsivity's facets rather than the broader impulsivity construct as a total score) and various neuropsychological laboratory behavioral measures (Conners Continuous Performance Task [CCPT] and Iowa Gambling Task) in 127 neurotypical participants. Lage et al. (2012) found no association between candidate gene 5-HTTLPR and BIS-11 non-planning and attentional impulsivity facets of impulsivity but noted sensitivity due to the behavioral (neuropsychological) measure used.

Carrying the endophenotype concept to behavioral phenotypes, the BIS-11 has been used to evaluate impulsivity and its BIS-11 facets as candidate endophenotypes (together a deep endophenotype). For example, Lombardo et al. (2012) used the BIS-11 to study trait impulsivity

as a candidate endophenotype for bipolar disorder in 54 clinical participants, 57 non-clinical siblings, and 49 controls. Across scores for total impulsivity and all three BIS-11 factors of motor impulsivity, attentional impulsivity, and non-planning impulsivity, mean scores for clinical participants was statistically higher than for non-clinical siblings, whom had statistically higher scores than controls across the board (Lombardo et al., 2012). These results confirmed impulsivity and each of its BIS-11 facets candidate endophenotype status (Lombardo et al., 2012).

Motor Impulsivity. Motor impulsivity (rapid-response impulsivity) is a facet of trait impulsivity and the focus of this study. It is one of three types of trait impulsivity measured by the BIS-11. As suggested previously, it can be defined as behavior without forethought (Hamilton et al., 2015; Jauregi et al., 2018). It is the observable form of impulsivity. It is an act, a motor action that can be a product of other, latent forms of impulsivity, such as choice impulsivity and cognitive impulsivity, or can symptomatically exacerbate their impact. In the context of its operational observable behavioral embodiment, it has been defined as a deficiency in prepotent response inhibition (Jauregi et al., 2018). More generally, as suggested previously and below, it can be operationalized via a deficit in behavioral response inhibition (disinhibition) of which prepotent response inhibition is a component. In the context of the above discussion, one way to view motor impulsivity versus deficits in behavioral response inhibition is as a form of trait impulsivity versus as a form of state impulsivity, to the extent that the former is measured using self-report measures and the latter is measured using behavioral (cognitive) laboratory measures.

Trait measures of motor impulsivity include the motor impulsivity scale of the BIS-11 (Patton et al., 1995), which was used in this study. Laboratory behavioral measures of motor impulsivity are focused on measurement of deficits in behavioral response inhibition (discussed next). A decade ago, the International Society for Research on Impulsivity (InSRI) compared the validity, reliability, and dimensional sensitivity of a plurality of laboratory behavioral measures of motor impulsivity and identified two neurobiologically and conceptually distinct subtypes of motor impulsivity (rapid response impulsivity) that can be measured using laboratory behavioral measures: prepotent response inhibition and prepotent response extinction (used as a term for the purposes of this study; Chamberlain & Fineberg, 2015; Hamilton et al., 2015). These two facets directly map onto the first two facets of the three facets described by Barkley's theory of inhibitory deficits discussed previously. Among the measures evaluated, the go/no-go task was identified as a possible measure of prepotent response inhibition and the stop-signal task a measure of prepotent response extinction (Hamilton et al., 2015). Each of these is discussed in more detail in the next section. The InSRI, however, did not identify which subscales of the above measures best segregate these two factors or optimize the discriminant validity of both measures (a goal of this study) and what neurobiological measures then correlate with those subscales (Hamilton et al., 2015).

As described previously and later in this chapter, neurobiological correlates of impulsivity and behavioral response inhibition include units of measure along RDoC's scale agnostic continuum. Such neurobiological measures include functional neuroimaging that identifies key brain regions, neurophysiological measures that identify implicated neural network circuits, and behavioral, psychiatric, and molecular genetics methods that link genetic liability to those neurobiological measures, self-report, and laboratory behavioral measures, and ultimately,

to behavioral phenotypes. The neurobiological distinctions between prepotent response inhibition and prepotent response extinction include unique brain regions and neural circuits as identified by fMRI studies, for example (Chamberlain & Fineberg, 2015; Hamilton, 2015). These are discussed in detail later in this chapter.

From the perspective of motor impulsivity per se—that is to say, as a form of trait impulsivity—motor impulsivity has distinct neurobiological neural network circuit correlates than either attentional impulsivity or non-planning impulsivity (Ai et al., 2019). For example, Ai et al. (2019) used structural magnetic resonance imaging (a neuroimaging measure) to measure gray matter volume in the brain of 84 neurotypical participants segregated by BIS-11 total scores (combining the attentional, non-planning, and motor impulsiveness subscale scores) and individual subscale scores. The authors observed decreased gray matter volume in the supplementary motor area (SMA) and paracentral lobule (PCL) correlated with high BIS-11 motor impulsivity sub-score, but not with attentional or non-planning impulsivity sub-scores. PCL activation, for example, is commonly deficient in ADHD patients where impulsivity is the seminal deficit (Robbins et al., 2012). Even at the neuropsychological level, authors such as Bakhshipour et al., (2020) have observed marked differences in laboratory behavioral measures of motor impulsivity between ADHD patients and normal controls with ADHD patients showing marked differences in motor impulsivity but not choice impulsivity. This is an example of the potential unique transdiagnostic importance of motor impulsivity versus other types of impulsivity.

Synthesis of Measures and Dimensional Models of Impulsivity. Impulsivity as a latent construct can be parsed or decomposed into many different measurable variables as is suggested by its many definitions in the literature to comprise a deep endophenotype of impulsivity. These variables can be facets, features, components, phase states, subsets, lower order factors, and endophenotypes of the broader construct or endophenotype of trait impulsivity. Such variables include countervailing variables to impulsivity (disinhibition), such as impulse control (response inhibition). In the case of this study, behavioral response inhibition (BRI) was the focus, and, more particularly, two facets of behavioral response inhibition were of interest to measure. These facets comprise two of the three facets described by Barkley (1997a) in a previous section of this chapter, namely, inhibition of a prepotent response, referred to in this study as prepotent response inhibition, and inhibition of an ongoing response, referred to in this study as prepotent response extinction.

Operationally, impulsivity was measured in this study via self-report measures using the most widely used and validated psychometric instrument to measure trait impulsivity, the Barratt Impulsiveness Scale version 11 (BIS-11), which, as described above, comprises 30 questions that measure six impulsivity first order factors: attentional impulsiveness, motor impulsiveness, self-control, cognitive complexity, perseverance, and cognitive instability; that comprise three second order factors (subtraits): non-planning impulsiveness (lack of premeditation or precognition), motor impulsiveness (action without thought), and attentional impulsiveness (the ability to concentrate; Coutlee et al., 2014; Patton et al., 1995; Stanford et al., 1999).

Behavioral Response Inhibition

The notion of impulsivity as lack of self-control implies a means to control or inhibit impulsive urges (motor actions), that is, behavioral inhibition (impulse control or motor response inhibition). Indeed, self-control, including impulse control and behavioral response inhibition (under the cognitive control subdomain in the RDoC matrix), is often considered a key executive function (Anokhin et al., 2017; Barkley, 2005; Nash et al., 2013; Stahl & Mignon, 2011; Wilburtz et al., 2014; Wright et al., 2014; Xia et al., 2020). Others do not consider behavioral inhibition an executive function per se, but a seminal predicate to proper executive functioning, providing a delay (cognitive moment) to enable executive control to properly engage and function (Barkley, 2016). Therefore, as discussed previously, lack of, or a deficiency in, behavioral response inhibition (i.e., disinhibition) can also be considered a facet of impulsivity or its operational equivalent. As inhibition suggests an observable response (motor action) to an external (exogenous) stimulus or internal (endogenous) cognition, behavioral (or motor) response inhibition (BRI) is a more complete term (Aron & Poldrack, 2005; Barkley, 2005; Bhaijiwala, 2016; Congdon, 2008; Congdon et al., 2014; Hoyniak & Petersen, 2019; Schachar et al., 2007; Skippen et al., 2020; Verbruggen & Logan, 2009). After all, one can have impulsive thoughts without acting on them and action implies behavior via a motor response.

In addition to being described as a facet of impulsivity or as the operational embodiment of impulsivity, behavioral response inhibition (BRI) is often described as the behavioral component of impulsivity (Ditrich et al., 2021) and impulsivity described as the consequence of impaired BRI (Bari & Robbins, 2013). In other words, the impulsive cannot inhibit their maladaptive hasty predilections. Consequently, BRI can be defined as

the ability to suppress a prepotent or habitual response, including both motor actions and higher-order responses (such as thoughts, memories, or emotions) and is therefore critical to the ability to stop or suppress rapid, automatic behaviors in response to goals environmental contingencies (Congdon et al., 2010, p. 2).

BRI is also heritable, making it a putative endophenotype for psychiatric illnesses (DSM mental disorders; Anokhin et al., 2017; Schachar et al., 2011; Wright et al., 2014).

As with impulsivity, behavioral response inhibition has been the subject of a plurality of definitions in the literature including: (a) a combination of three interdependent processes (i) inhibition of an initial prepotent response to an internal or external stimulus; (ii) inhibition of an ongoing response to an internal or external stimulus so as to permit a delay (i.e., a cognitive moment) in the decision to respond; and (iii) the ability to maintain the period of delay including self-directed responses necessary to deflect competing events and responses (interference control; Bickel et al., 2012); (b) “ability to control potentially interfering thought processes and actions” (Carlson & Wang, 2007, p. 489), (c) inhibition or withholding of a motor response (Garon et al., 2008), (d) comprising “withholding/delay of prepotent or automatic responses” (simple response inhibition) and “holding a rule in mind, responding according to this rule, and inhibiting a prepotent response” (complex response inhibition; Garon et al., 2008, p. 36); (e) “one’s ability to deliberately inhibit dominant, automatic, or prepotent responses when necessary” (Miyake et al., 2000, p. 57); (f) “the cognitive-related ability to inhibit a strong dominant response in favor of a subdominant one” (Ginexi & Robertson, 2011, p. 5), (g) “the suppression of actions that are inappropriate in a given context and that interfere with goal-driven behavior” (Mostofsky & Simmonds, 2008, p. 751), (h) “the ability to suppress or ignore information irrelevant for the achievement of a particular goal” (Velasquez et al., 2017, p. 65), (i)

the ability to suppress behaviors that are inappropriate, unsafe, or no longer required (Chambers et al., 2009), (j) “the ability to suppress unwanted responses and to minimize the processing of irrelevant information while selecting relevant information for further processing and responding” (Ettinger et al., 2018, p. 484); and (k) the “process of suppressing behaviour which is premature, undesirable, or dominant and subjectively desirable but leads to negative consequences” (Hlavata et al., 2018, p. 44).

One commonality implied by and synthesized from most definitions of BRI and explicitly stated in others, such as Barkley (2016), is a fragmentation of elements of behavioral response inhibition that can be described as (i) inhibition of an initial primed or prepotent response to an internal or external stimulus temporally sufficient to decouple the stimulus from the response to it and permit prefrontal cortical processing (i.e., executive functions) to evaluate the appropriateness of the response (the cognitive moment) in light of other stimuli or information (termed here prepotent response inhibition), (ii) interruption of an ongoing response to a given internal or external stimulus temporally sufficient to decouple the stimulus from the response to it and permit prefrontal cortical processing (i.e., executive functions) to re-evaluate the appropriateness of continuing the response and extinguish the prepotent response, if necessary, in light of other stimuli or information (termed here prepotent response extinction), and (iii) shielding the prefrontal cortical processing and consequential behavior informed by that processing from interruption, interference, distraction, and disruption from competing events, stimuli, and cognitions (referred to above as interference control).

Thus, where impulsivity, and particularly motor impulsivity, can be described as an action (behavior without forethought), behavioral response inhibition can be described as affirmative inaction or interruption of an action in favor of cognitive processing to evaluate the

appropriateness of the action. As a variable of the construct of impulsivity, lack of behavioral response inhibition (disinhibition) or a deficit in the behavioral inhibition system (BIS) can enable or increase impulsivity via the behavioral activation system (BAS) and, consequently, as a more descriptive construct, is more measurable. An overactive behavioral activation system or an underactive behavioral inhibition system associates with impulsivity and an overactive behavioral inhibition system and underactive behavioral activation system associates with, for example, anxiety (Wright et al., 2014).

Prepotent Response Inhibition

Action restraint is often termed prepotent response inhibition. It can be described as inhibition of a primed prepotent (e.g., habitual or automatic) response to a thought (endogenous cognition) or to an external stimulus (Eagle et al., 2005; Ettinger et al., 2018; Hong et al., 2024; Korolczuk et al., 2018; MacKillop et al., 2016; Miyake et al., 2000; Schachar et al., 2007; Sebastian et al., 2013; Shi et al., 2020; Sperl et al., 2021; Stahl et al., 2014; Tiego et al., 2018; Torenvliet et al., 2023; Wessel, 2017; Zhang et al., 2024). Thus, prepotent response inhibition as a term describing a particular endophenotype of impulsivity and lower order factor of behavioral response inhibition is a putative variable that comprises the first element of behavioral response inhibition noted above—that is, inhibition of a prepotent response. Deficits in prepotent response inhibition are typically referred to as waiting impulsivity (Hlavata et al., 2018). To the extent prepotent response inhibition can be differentially measured, it can serve as a distinct measurable variable that may, for example, be differentially measurable with laboratory behavioral instruments, such as the go/no-go task (GNG) and Conners continuous performance test (CCPT; Hlavata et al., 2018; Hong et al., 2024; Torenvliet et al., 2023; Wright et al., 2014; Zhang et al., 2024) or have a distinct waveform qEEG/ERP signature (Hong et al., 2024; Zhang

et al., 2024). Prepotent response inhibition has been shown to have unique neural circuit correlates from prepotent response extinction (Aziz-Safaie et al., 2024; Gholamipourbarogh et al., 2024; Schachar et al., 2011; Weber et al., 2023). Each of these measures, GNG measures and ERP components, are directly observable endophenotypes of latent variables of prepotent response inhibition or their neural correlates, which are endophenotypes in their own right, operationalized by their measures and comprising a deep endophenotype. Consequently, prepotent response inhibition may be neurobiologically, neuropsychologically, or symptomatically orthogonal to prepotent response extinction.

Prepotent Response Extinction

Action cancellation is referred to for the purposes of this study as prepotent response extinction. It can be described as inhibition of an ongoing response to an internal cognition or to an external stimulus, long enough to determine whether it is appropriate to continue to respond (Afonso et al., 2021; Aziz-Safaie, et al., 2024; Gholamipourbarogh et al., 2024; Schachar et al., 2007; Sebastian et al., 2013; Sperl et al., 2021; Stahl et al., 2014; Weber et al., 2023). Thus, prepotent response extinction was a term used in this study to describe a particular endophenotype of impulsivity and lower order factor of behavioral response inhibition as a putative variable that comprises the second element of behavioral response inhibition noted above—that is, inhibition of an ongoing response. While the term prepotent response extinction has not appeared in the literature before this study, because both action cancelation and action restraint directly relate to primed prepotent responses (as opposed to actions provoked by novel stimuli), it is arguably better to maintain that connection in terminology. Further, inhibition of an ongoing response suggests a similar process as inhibition of a prepotent response, but such is not the case (Gholamipourbarogh et al., 2024; Shachar et al., 2011; Weber et al., 2023). A better

description is that an ongoing response must be extinguished rather than inhibited, since it has already begun. This term also suggests a nexus to compulsivity. Deficits in prepotent response extinction are typically referred to as stopping impulsivity (Hlavata et al., 2018). To the extent prepotent response extinction can be differentially measured, it can also serve as a distinct measurable variable that may, for example, be differentially measurable with laboratory behavioral instruments, such as the stop-signal task (Aziz-Safaie et al., 2024; Gholamipourbarogh et al., 2024; Hlavata et al., 2018; Weber et al., 2023) or have a distinct waveform qEEG/ERP signature (Gholamipourbarogh, 2024). Both measures of the SST and ERP related ERP components and waveform complex have been identified as putative endophenotypes of psychiatric illnesses distinct from those related to the GNG task (Aziz-Safaie et al., 2024; Gholamipourbarogh et al., 2024; Schachar et al., 2011). They represent directly observable measures of latent variables (i.e., prepotent response extinction) that comprise endophenotypes. The SST has been shown to have its own unique neural circuit correlates (Aziz-Safaie et al., 2024; Gholamipourbarogh et al., 2024; Schachar et al., 2011; Weber et al., 2023). Consequently, prepotent response extinction may be neuropsychologically or symptomatically orthogonal to prepotent response inhibition.

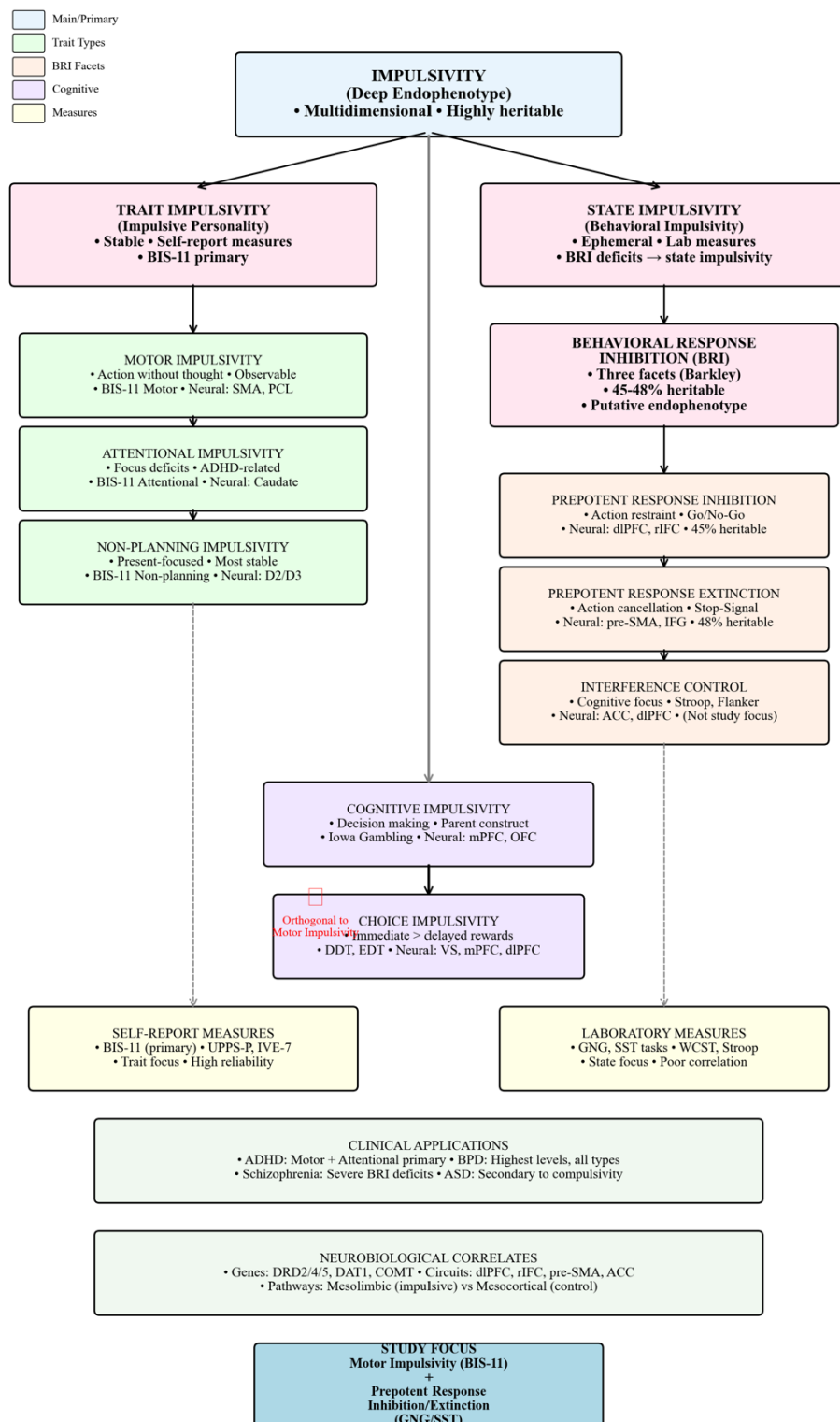
Interference Control

Interference control is the ability to deflect, ignore, or block competing thoughts (cognitions), distractions, and responses to enable goal directed behavior (Afonso et al., 2021; Ettinger et al., 2018; Friedman & Miyake, 2004; Sebastian et al., 2013; Sperl et al., 2021; Tiego et al., 2018). One can think of interference control's role in BRI as enabling the quiet necessary for a cognitive moment to occur directed at deciding whether to respond to a prepotent thought or stimulus or extinguish the response once started.

Applying the previously described taxonomies, the first two facets of BRI (prepotent response inhibition and prepotent response extinction) imply motor action, so their deficiency implies trait and state motor impulsivity, and the third facet (interference control) implies trait and state cognitive impulsivity. As suggested above, motor and cognitive impulsivity are thought to have generally distinct neurobiological correlates. Further, impulsive behavior is action that can be observed and is thus the dominant impulsivity facet in the DSM nosology. Consequently, this study focused on the first two facets of BRI and did not focus on interference control.

Measurement of Behavioral Response Inhibition

Operationally, behavioral response inhibition (BRI), or lack thereof (disinhibition), is a measurable facet of impulsivity and is commonly measured in the laboratory, rather than via a self-report measure, using the go/no-go task (GNG), which is arguably more appropriately considered a measure of prepotent response inhibition (the first facet of BRI) in that it requires the inhibition of a prepotent response; the stop-signal task (SST), which measures inhibition of an ongoing response that has already started (the second facet of BRI; Aziz-Safaie et al., 2024; DeYoung & Reuter, 2016; Dougherty et al., 2005; Weber et al., 2023) described here as prepotent response extinction, and the Simon task, flanker task, Stroop test, and antisaccade task, all which measure of the ability to filter out extraneous stimuli, the third facet of BRI (Tillman & Wiens, 2011). Each facet of BRI was treated as a subtype of behavioral response inhibition, and thus impulsivity, and consequently as a potential differentiable endophenotype, with prepotent response inhibition and prepotent response extinction being the particular focus of study here.

Figure 4*Hierarchical Structure of Impulsivity: Types, Subtypes, and Measurement Approaches*

DSM Nosology

Contrary to the syndromal transdiagnostic spectrum perspective of the RDoC that focuses of neurobiological and neuropsychological correlates of behavioral phenotypes as framed by the endophenotype hypothesis, the DSM focuses on an apparently, but artificially, definite categorical framework of symptoms (American Psychiatric Association, 2022). While behavioral phenotypes include categorical mental disorders, the RDoC focuses on their precursive psychological constructs, neurobiological underpinnings, and genetic origins, providing more primitive upstream agency that can be a focus of empirical inquiry (NIMH, n.d.). But the RDoC and DSM need not be mutually exclusive. Categorical reductionism can inform dynamical holism.

Consequently, below is a DSM focused summary of each behavioral phenotype that is the focus of the broader discussion and operational focus of this study regarding their relationship to deficits in behavioral response inhibition, at which they all merge to varying degrees in relation to shared symptomatic impulsivity. Each discussion includes a general description of each DSM disorder and RDoC informed discussion regarding etiology and neurobiological and genetic correlates. Comorbidities are also discussed as each of these disorders, more often than not, are comorbid with other DSM disorders, including each other. Such comorbidities are to be expected when they all share a common behavioral symptomatic correlate, impulsivity. The discussions that follow also include a discussion of the diagnosis and treatment of each disorder. This will provide a framework to inform the use of validated RDoC endophenotypes and deep endophenotypes, including those identified by this study, to both inform and supplement the DSM framework for differential diagnosis and for differential treatment in broader studies (see generic study exemplar below) and neurocomputational studies

(discussed in the last section of this chapter). For example, with a fundamental understanding of the current state of the art for a given diagnosis or treatment, the role of impulsivity and BRI and the facets that are the focus of this study can inform the state of the art of diagnosis and treatment to revise each in such a way that highlights identifying facet and deep endophenotype focused deficiency and treatment towards the specific facet.

ADHD

ADHD is an Axis I polygenic neurodevelopmental behavioral disorder of the central nervous system primarily characterized by varying degrees of inattention, impulsivity, and hyperactivity problems, alone or in combination, that is reported to affect as much as over 7% of children (Al Ghamdi & AlMusailhi, 2024; American Psychiatric Association, 2022; Aron & Poldrack, 2005; Asherson et al., 2007; Barkley, 2005; Bhajiwala, 2016; Congdon et al., 2014; Doyle et al., 2005; Faraone et al., 2003; Filipovska & Ajdinski, 2023; Frank-Briggs, 2011; Guo et al., 2024; Hayman & Fernandez, 2018; Hu et al., 2024; Krain & Castellanos, 2006; Schachar et al., 2007; Shen & Zhou, 2024; Sha & Sarkar, 2024; Stahl & Mignon, 2011; Volkow et al., 2009; Wu et al., 2023). Its prevalence has been reported as high as 8-15% (American Psychiatric Association, 2022; Faraone et al., 2003; Filipovska & Ajdinski, 2023; Perle & Vasilevskis, 2021). ADHD is characterized by the onset of symptoms prior to age seven, with about 50%-90% of cases continuing into adulthood with prevalence in the adult population reported at around 2.5% (Abdelnour et al., 2022; American Psychiatric Association, 2022; Filipovska & Ajdinski, 2023; Fank-Briggs, 2011; Gagnon et al., 2022; Hayman & Fernandez, 2018; Senkowski et al., 2023). ADHD is often co-morbid with both Axis I and Axis II disorders (American Psychiatric Association 2000; American Psychiatric Association, 2022; Frank-Briggs, 2011; Guo et al., 2024; Hayman & Fernandez, 2018; Scheerer et al., 2024). ADHD occurs at

least twice and as much as four times as frequently in boys than it does in girls (Abdelnour et al., 2022; American Psychiatric Association, 2022; Hayman & Fernandez, 2018). Over the years and throughout the DSM's evolution, the characterization of the disorder, classification, and diagnostic criteria have evolved to both broaden its scope and concentrate its focus.

Classification and Diagnosis of ADHD. In 2011, the American Academy of Pediatrics (AAP) provided a guideline and set of policies to enable clinicians to diagnose ADHD in children ages 6-12, noting three key elements necessary for proper diagnosis: (a) the explicit use of the DSM criteria, (b) the gathering of details of the child's symptomatic behavior from multiple settings, such as home and school, and (c) evaluation for comorbid conditions that may complicate diagnosis and treatment (Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management, 2011). The DSM-5-TR provides a list of nine symptoms for inattention (Group 1) and nine for hyperactivity-impulsivity (six for hyperactivity and three for impulsivity; [Group 2]; American Psychiatric Association, 2022). It further provides that such symptoms must have persisted for at least six "months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities" (American Psychiatric Association, 2022, p. 69). These two groupings are the basis of the three subtypes of ADHD, predominantly inattentive type, predominantly hyperactive-impulsive type, and combined type. The use of artificial intelligence methods, including machine learning and deep learning, for classification of ADHD is discussed later in this chapter in the section discussing neurocomputational methods.

Predominantly Inattentive Type. ADHD predominantly inattentive type is the most prevalent presentation of the disorder in women (Galvez-Contreras et al., 2022). For a diagnosis of ADHD-inattentive subtype (previously referred to as ADD; see below), the DSM-5-TR

requires six or more of nine symptoms from the inattentive domain (Group 1) that constitute a majority of symptoms (American Psychiatric Association, 2022; Frank-Briggs, 2011). Children with inattentive type are often forgetful and present as unfocused and easily distracted and, consequently, appear unable to listen when spoken to and struggle to follow directions, complete tasks, or master new concepts that require longer attention (American Psychiatric Association, 2022; Frank-Briggs, 2011). Such children may comprise the group often considered the day dreamers in school.

Predominantly Hyperactive-Impulsive Type. ADHD predominately hyperactive/impulsive type is equally distributed between men and women, but the most common diagnosis in pre-school children (Galvez-Contreras et al., 2022). For a diagnosis of ADHD-primarily hyperactive-impulsive subtype, the DSM-5-TR requires six or more symptoms from the hyperactive-impulsive domains (Group 2) with fewer than six from inattentive domain (Group 1; American Psychiatric Association, 2022; Frank-Briggs, 2011). Children with the predominantly hyperactive-impulsive subtype are in constant motion, often restless, fidgeting, highly energetic, loquacious, and struggle to sit still or perform quiet tasks (the hyperactive domain) and are prone to acting out and reacting with absence of forethought by making and displaying ill-timed or socially inappropriate interruptions, remarks, or emotions, often in response to exaggerated impatience and frustration with such things as waiting their turn or for a reward or something they desire (the impulsive domain; American Psychiatric Association, 2022; Frank-Briggs, 2011). Such children are often characterized disruptive or lacking in self-control in school.

Combined type: Inattentive Type with Hyperactivity-Impulsivity. ADHD combined type is the most common presentation of the disorder in men (Galvez-Contreras et al., 2022). For a diagnosis of ADHD combined subtype, the DSM-5-TR requires six or more of nine symptoms from each of the inattentive domains (Group 1) and the hyperactive-impulsive domains (Group 2; American Psychiatric Association, 2022). The combined type of ADHD accounts for a majority of diagnoses, particularly in boys (American Psychiatric Association, 2022; Frank-Briggs, 2011). Children with the combined subtype are often hyperbolically characterized as completely out of control in school.

Etiology of ADHD. The causes of ADHD have been described to include genetics (nature; discussed below) and environment (nurture; Shen & Zhao, 2024). Environmental factors have been described to include tobacco smoke during pregnancy, low birth weight, and degree of prematurity (American Psychiatric Association, 2022; Frank-Briggs, 2011; Hayman & Fernandez, 2018; Shen & Zhao, 2024) and food additives, the latter of which has received much media attention, but has been largely disproven (see Biederman & Faraone, 2005). While the genetic etiology of ADHD has been better characterized, a review of the literature suggests that environmental factors are relatively more evasive to characterize.

Pathophysiology of ADHD. Neuroimaging studies, including diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), and functional near infrared spectroscopy (fNIRS) studies, have described abnormal morphology and dysfunction in frontoparietal, frontostriatal, and frontocerebellar neural network circuits and neuroanatomical loci in the medial prefrontal cortex and posterior cingulate cortex implicated in executive functions as well as the caudate nucleus and putamen, default mode network (DMN), among others (Gagnon et al., 2022; Özkan & Haznedaroğlu, 2023; Shen & Zhou, 2024). These dopaminergic neural circuits

and regions implicate dopamine as well as norepinephrine and serotonin receptors (Gagnon et al., 2022; Özkan & Haznedaroğlu, 2023). Neuropsychological studies have suggested that the left frontal lobe of the brain of children with ADHD is of lower volume than that of controls (Hayman & Fernandez, 2018; Krain & Castellanos, 2006; Özkan & Haznedaroğlu, 2023). This appears consistent with common theories concerning the role of the prefrontal cortex enabled executive function in impulse control associated with ADHD (see Barkley, 2005; Özkan & Haznedaroğlu, 2023; Stahl & Mignon, 2011). While not apparently definitive, the literature suggests that impulse control, and thus executive function, may be the most critical domain of the ADHD behavioral spectrum.

Current Treatment Paradigms for ADHD. Because ADHD is the most commonly diagnosed psychiatric disorder in children (American Psychiatric Association, 2022), treatment approaches may not consider a more complex and dynamic treatment paradigm. ADHD alone, that is, without a comorbid disorder, is found in only about one-third of children with the disorder (American Psychiatric Association, 2022; Franks-Briggs, 2011; Guo et al., 2024) and 20% in adults with ADHD (Taylor et al., 2022) suggesting caution when considering treatment of ADHD as a stand-alone disorder. Nonetheless, treatment of ADHD is multidimensional and involves coordination of behavioral, therapeutic, and drug interventions (Gagnon et al., 2022).

Behavioral. Behavioral interventions for ADHD include coordination of school-based interventions with proper management and training of parental interventions (Galvez-Contreras et al., 2022; Pierce, 2011). Since school settings are a logical environment where ADHD symptoms manifest to the point of functional impairment, teachers, rather than parents, become the first responders and front line in dealing with the disorder, since parents may be more tolerant of maladaptive behaviors of their children (Galvez-Contreras et al., 2022).

Psychotherapy. Psychotherapeutic interventions for ADHD include cognitive behavioral therapy and family therapy (Frank-Briggs, 2011; Galvez-Contreras et al., 2022; Hayman & Fernandez, 2018; Sapkale & Sawal, 2023). Such treatment is likely to be initially responsive to input from schools, through school psychologists, to parents, to a child psychologist for treatment, and in coordination with a psychiatrist for neuropharmacological treatment (Galvez-Contreras et al., 2022). Whereas a psychologist may serve as an intermediary for children with ADHD and a psychiatrist holding a key role in ongoing evaluation, in adults the opposite may be true (Galvez-Contreras et al., 2022; Perle & Vasilevskis, 2021; Taylor et al., 2022).

Psychopharmacology. Psychopharmacology is the first line treatment for ADHD, particularly in children (American Psychiatric Association, 2022; Galvez-Contreras et al., 2022). Psychopharmacological interventions for ADHD focus on increasing levels of key neurotransmitters associated with arousal, namely dopamine and norepinephrine (serotonin is also relationally implicated), which can be accomplished by either increasing their neuronal release or inhibiting their neuronal reuptake and can be either stimulant or non-stimulant based (Galvez-Contreras et al., 2022; Hayman & Fernandez, 2018; Stahl & Mignon, 2011). The choice and progress of psychopharmacological treatment is governed by patient response, tolerance of the effective dose, abuse potential, and progression of treatment (Galvez-Contreras et al., 2022). Stimulant therapy for ADHD was described as early as 1937 (Patrick et al., 2009) and accounts for about two-thirds of pharmaceutical treatment in children (Galvez-Contreras et al., 2022; Gagnon et al., 2022; Sapkale & Sawal, 2023; Stahl & Mignon, 2011). Current stimulants include central nervous system (CNS) stimulant and norepinephrine-dopamine reuptake inhibitor (NDRI) methylphenidate (Ritalin, Focalin, Concerta, Metadate), mixed amphetamine salts (Adderall), lisdexamfetamine (Vyvanse), and dextroamphetamine (Dexedrine; Frank-Briggs,

2011; Galvez-Contreras et al., 2022; Hayman & Fernandez, 2018; Stall & Mignon, 2011).

Adverse events in children include weight loss due to appetite suppression (Pierce, 2011), but most controversial is the potential for abuse (Biederman & Faraone, 2005; Galvez-Contreras et al., 2022; Stahl & Mignon, 2011; Pierce, 2011), particularly when prescribed to children.

Non-stimulant therapy includes atomoxetine (Strattera, Attentin), guanfacine (Intuniv), bupropion (Wellbutrin, Zyban), and modafinil (Provigil; Galvez-Contreras et al., 2022; Gagnon et al., 2022; Hayman & Fernandez, 2018; Sapkale & Sawal, 2023; Stahl & Mignon, 2011) and are often prescribed as second-line psychopharmacological treatments to non-responders to stimulant therapy (Frank-Briggs, 2011; Galvez-Contreras et al., 2022) or where there is potential for abuse or contraindications for comorbid disorders (Galvez-contreras et al., 2022; Stahl & Mignon, 2011). Atomoxetine (a selective norepinephrine reuptake inhibitor [NRI]) is the most popular and often a first line treatment in adults, who account for approximately two-thirds of atomoxetine prescriptions (Galvez-Contreras et al., 2022; Gagnon et al., 2022; Hayman & Fernandez, 2018; Stahl & Mignon, 2011). Because atomoxetine has adrenergic mechanistic properties, adverse events include hypertension.

Comorbidities of ADHD. About two-thirds of children diagnosed with ADHD are also diagnosed or diagnosable with one or more comorbid disorders (Frank-Briggs, 2011; Galvez-Contreras et al., 2022; Gagnon et al., 2022; Guo et al., 2024; Hayman & Fernandez, 2018; Scheerer et al., 2024; Shen & Zhou, 2024). The most common comorbidities in children include oppositional defiant disorder (ODD) and conduct disorder (CD; which can be found in 50% of school-aged children with ADHD), bipolar disorder, anxiety disorders, learning disabilities, and tic disorders (TD) and restless leg syndrome (American Psychiatric Association, 2022; Galvez-Contreras et al., 2022; Guo et al., 2024; Hayman & Fernandez, 2018; Shen & Zhou, 2024; Stahl

& Mignon, 2011). Epilepsy is also relatively often comorbid with ADHD, in large part, it is thought, due to high genetic correlation implicating SLC6A1 and SLC9A9 genes and associated dopaminergic dynamics (Shen & Zhou, 2024). As mentioned previously, prior to the DSM-5, ASD and ADHD could not be diagnosed as comorbid disorders (Abdelnour et al., 2022; American Psychiatric Association, 2000; American Psychiatric Association, 2022; Waldren et al., 2024). As much as 14%-50% of ADHD patients have co-morbid ASD (Abdelnour et al., 2022; Al Ghamdi & AlMusailhi, 2024; Bougeard et al., 2021; Lin et al., 2024; Scheerer et al., 2024; Shen & Zhou, 2024). This shift in the latest iteration of the DSM may have contributed to increasing prevalence of ADHD and has contributed to criticisms of overdiagnosis discussed below, since ADHD and ASD were previously mutually exclusive. Whether a comorbid disorder is brought to clinical levels by ADHD or vice versa appears difficult to resolve at this time.

Adults diagnosed with ADHD for the first time, and thus not treated during childhood, exhibit higher incidence (as high as 80%) of comorbid disorders than adults diagnosed and treated during childhood (Choi et al., 2022; Galvez-Contreras et al., 2022; Hayman & Fernandez, 2018; Stahl & Mignon, 2011; Wilens et al., 2004), even notwithstanding a then current presentation of ADHD-in remission and thus not meeting the DSM criteria at the time of the ADHD diagnosis based on retrospective evaluation (Abelnour et al, 2022; Faraone et al., 2006; Taylor et al., 2022). Most common among these are anxiety disorders, depression, bipolar disorder, substance use disorders, and personality disorders, including anti-social personality disorder and borderline personality disorder (Choi et al., 2022; Galvez-Contreras et al., 2022; Sapkale & Sowal, 2023; Sobanski, 2006, Stahl & Mignon, 2011). Since numerous psychiatric disorders in adults (e.g., personality disorders) are not typically diagnosed in children and vice

versa, it appears difficult to correlate the incidence of particular comorbidities across the two populations.

Diagnosis and Treatment of ADHD and Comorbid Disorders. The presence of one or more comorbid disorders can complicate diagnosis of ADHD due to either symptomatic homology or symptomatic masking (Sapkale & Sawal, 2023; also see Stahl & Mignon, 2011). Comorbidities also complicate the ADHD treatment paradigm as, while there could be overlap in symptoms, there could also be contraindication in psychopharmacological treatment, as to type of medication, dose, or release profile (Al Ghamdi & AlMusailhi, 2024; Gagnon et al., 2022; Sapkale & Sawal, 2023; Stahl & Mignon, 2011).

Adult ADHD. About 50%-90% of children diagnosed with ADHD will persist with the disorder into adulthood (Abdelnour et al., 2022; Hayman & Fernandez, 2018; Stahl & Mignon, 2011), although symptoms tend to decline with age to the point where an adult diagnosed as a child would not meet the DSM criteria as an adult (Biederman & Faraone, 2005; Galvez-Contreras et al., 2022; Özkan & Haznedaroğlu, 2023). Generally, diagnosis for adults depends on retrospective review of childhood behaviors and use of self-report measures, such as the Conners rating scale (Wilens et al., 2004). Gradual evaporation of symptoms, as children grow into young adults and mature into older adults, and the imprecise nature of retrospective evaluation of adults not previously diagnosed as children, suggests a potential for misdiagnosis or overdiagnosis and has helped enable much controversy and debate whether ADHD is a legitimate disorder or fabricated by an insidious array of stakeholders in its diagnosis and treatment (Abdelnour et al., 2022; Özkan & Haznedaroğlu, 2023). This issue is discussed after the next section on heritability of ADHD.

Heritability and Candidate Genes of ADHD. As mentioned previously in this chapter in the discussion of psychiatric and molecular genetics, the heritability of ADHD is very high, as much as 74%-88% (Barkley, 2005; Faraone & Larsson, 2019; Krain & Castellanos, 2006; Sandin et al., 2017; Shen & Zhou, 2024; Stahl & Mignon, 2011). Lack of impulse control is one of the earliest indicators of ADHD to manifest and impulsivity is a key criteria of its DSM nosology (American Psychiatric Association, 2022). Consequently, impulsivity and BRI serve as candidate endophenotypes for ADHD and understanding their genetic correlates (genetic etiology) is of interest.

The literature indicates that ADHD is both polygenic and heterogenic (Doyle et al., 2005). At least nine genes have been implicated: dopamine (D) transporter gene 1 (DAT 1, SLCA3), D4 receptor (DRD4), including the DRD4-7R allele, D5 receptor (DRD5), D beta hydroxylase enzyme (DBH), alpha 2A receptor (ADRA2A), the synaptic protein gene (SNAP25), the 5HT transporter gene (5HTTLPR), the serotonin 1B receptor (HTR1B), norepinephrine transporter (NET, SLC6A2), and the fatty acid desaturase 2 enzyme gene (FADS2, Doyle et al., 2005; Shen & Zhou, 2024; Stahl & Mignon, 2011; Volkow et al., 2009). Table 3 summarizes these genes. However, each gene has a relatively small effect size (weak effect, Volkow et al., 2009). In addition to the missing heritability problem discussed earlier in this chapter, this may be due, in part, to the number of DSM symptoms and the large number of their different combinations. That suggests that different risk genes or alleles impart liability, or at least stronger liability, on different symptoms, such as impulsivity, BRI or its facets, or combinations of symptoms, rather than on the behavioral phenotype as a whole.

Table 3*Select Candidate Genes for ADHD*

Gene/Allele	Function
DAT1 (SLC6A3)	Dopamine Transporter
DRD4-7R VNTR*	Dopamine Receptor
DRD5	Dopamine Receptor
SNAP25	Synaptic Protein
5-HTTLPR*	Serotonin Transporter
HTR1B	Serotonin 1B Receptor
NET (SLC6A2)	Norepinephrine Transporter
FADS2	Fatty Acid Desaturase

Note: Table does not list all candidate (risk) genes for ADHD from the literature, only those discussed in this chapter.

*Shared select candidate gene with borderline personality disorder.

Evolving Nosology of ADHD: Misdiagnosis, Overdiagnosis, Underdiagnosis. One downside of the categorical nosology of the DSM (and categorical distinctions generally) is that the categories themselves are arguably arbitrary and are not static; they evolve over time through revisions of the DSM. This has led to controversial variation and scope creep with respect to the distinction between clinical and non-clinical categorical membership. What in one revision of the DSM is non-clinical, in another is diagnosis of a given DSM disorder and vice versa. This has made it difficult to conduct longitudinal studies and has caused controversy regarding over-

diagnosis and misdiagnosis, an issue exacerbated by comorbidities that share symptoms, such as impulsivity. ADHD, in particular, has been the subject of such controversy.

As previously mentioned, ADHD is currently the most often diagnosed psychiatric disorder in children (Abdelnour et al., 2022). Many observers have argued that diagnosis of ADHD in children has become so ubiquitous as to shift what was once normal behavior into a disorder treated by dangerous drugs and that such diagnosis is fueled by the pharmaceutical industry and insurance companies (Abdelnour et al., 2022). The debate has overflowed to adult diagnosis and treatment as well, with the media and many general medical practitioners questioning the science and motivations behind the apparent emergence of ADHD as a disorder and its pervasive stimulant psychopharmacological treatment (Abdelnour et al., 2022; Taylor et al., 2022). This has resulted in organization of opposition to the recognition of ADHD as a disorder, and even if so recognized, the relevance and utility of its diagnosis and treatment. Stolzer (2007), for example, represents a long held common thread of skepticism among the oppositional observers. He noted that in 1970 only about 2,000 children were diagnosed as “hyperactive” in the United States, whereas by 2006, close to ten million had been diagnosed with ADHD. Stolzer (2007) further argued that children in the United States are diagnosed at a greater frequency than in other countries and that ADHD has, suspiciously, only been described fairly recently. He also criticized the subjective nature of ADHD diagnosis. Additionally, Stolzer (2007) argued that there is no scientific evidence to support the biological basis of the disorder as a consequence of abnormal neurotransmitter release and circulation. Finally, Stolzer (2007) noted that methylphenidate has been likened neuropharmacologically to cocaine by the American Psychiatric Association and he further noted that its mechanism of action is unknown for ADHD. Over a decade ago, Connor (2011) noted a mix of factors that have contributed to an

increase of stimulant prescriptions for ADHD in the United States including the passage of new laws to incentivize the development of psychopharmacological treatments for children and the insurance and pharmaceutical industries exploiting those laws to expand their markets for stimulants.

While a literature review identified a wealth of material questioning the legitimacy ADHD as a psychiatric diagnosis and expressing concern regarding treatment paradigms, there was a dearth of academic literature with equal animation. A majority of the academic literature reviewed focused less on the legitimacy of ADHD as a disorder, and more on questions with respect to its subjective diagnostic criteria, treatment paradigms, and comorbidity challenges (Abdelnour et al., 2022; Choi et al., 2022; Sapkale & Sawal, 2023; Taylor et al., 2022).

The Stolzer (2007) and Connor (2011) references do, however, appear to present a fair representation of the most aggressive opposition to ADHD as a legitimate disorder in the academic literature. Critical consideration of several of the arguments presented by Stolzer and summarized by Connor provides perspective on the veracity of the arguments claiming ADHD to be the product of pseudoscience and economic opportunism. Stolzer (2007) argued that ADHD was a recent phenomenon in 2007, virtually appearing from nowhere. While ADHD, as a formal psychological term, can be traced to 1987 with its introduction into the DSM-III-R and latter editions, prior conditions that arguably encompassed the disorder trace back at least hundreds of years. For example, Palmer and Finger (2001) noted a description of ADD (ADHD inattentive-type) in a book written by Sir Alexander Crichton in 1798 where he characterized the disorder as “mental restlessness.” In 1902, Sir George Frederick Still described a disorder characterized by hyperactivity and impulsivity (Abdelnour et al, 2022; Connor, 2011). In the 1970’s, “hyperactivity” was used (Abdelnour et al., 2022, p. 469). ADD appeared in the DSM-III in 1980

as attention deficit disorder (ADD) with or without hyperactivity, before it was replaced by the descriptor ADHD in 1987 (Abdelnour et al., 2022). Consequently, the argument that the disorder has only been identified recently is spurious as, generally, only the name is recent, but not the disorder.

Stolzer's (2007) arguments that there is no scientific evidence to support the biological basis of the disorder are also highly suspect. A wealth of apparent well-reasoned studies (including RDoC studies) and analysis, including those described here, were found in the literature supporting the various biologically based etiologies regarding atypical neurotransmitter release and reuptake as correlated with ADHD symptoms and treatment outcomes (Faraone & Larsson, 2019; Hayman & Fernandez, 2018). Furthermore, Stolzer's notation that the American Psychiatric Association likened methylphenidate neuropharmacologically to cocaine does not account that such statement, if true, may have focused on a dose subject to abuse and addiction far above the therapeutic dose for ADHD. Finally, his argument that the mechanism of action of methylphenidate is unknown is arguably irrelevant. As many as 20% of drugs on the market today have unknown mechanisms of action (Davis, 2020). The arguments of the opposition literature summarized by Conner (2011) regarding the pharmaceutical and insurance industries fail to note that two industries availing themselves of laws that permit extension of their markets into pediatrics, ignoring other factors, suggests nothing more than rational economic behavior.

However, both Stolzer (2007) and Conner (2011) do present some compelling criticisms against the subjective nature of ADHD diagnosis and nature of treatment paradigms. Various epidemiological studies have suggested that ADHD may be over diagnosed if a diagnosis does not implicate functional impairment (Abdelnour et al., 2022; Biederman & Faraone, 2005; Fresson et al., 2019). Indeed, if a patient meets the DSM criteria for an ADHD subtype, but there

is no evidence of functional impairment, one may question what disorder there would be that needs treatment and why (Choi et al., 2022). However, if a patient meets the criteria, but has no functional impairment due to effective adaptation of coping mechanisms to overcome any impairments from the disorder that may adversely impact functioning, it is still arguably a disorder. Consider a patient with a traumatic brain injury that presents as behaviorally normal, but fMRI scans demonstrate complete loss of use of a portion of the brain. Yet adaptive neuronal pathway regeneration and redirection compensate for lost brain activity. Such a patient would still have traumatic brain injury but would present as not functionally impaired. This suggests some imprecision to the AAP guidelines described above.

Additionally, the DSM symptomatic criteria may be too open for a disorder with such complex and relational behavioral symptoms. The DSM also provides no baseline guidelines for normal developmental levels of the criteria against which to compare (see Biederman & Faraone, 2005; Taylor et al., 2022). This may contribute to overdiagnosis by those clinicians who do not come across the disorder with regularity (an issue common across many behavioral phenotypes, including ASD and more rare borderline line personality disorder [BPD] and schizophrenia discussed in the coming sections). In children, the disorder is diagnosed by pediatricians, child psychiatrists, and child psychologists (Stahl & Mignon, 2011; Perle & Vasilevskis, 2021). Pediatricians and school psychologists, who may not frequent diagnosis of psychiatric disorders in children, would likely depend on the DSM criteria to compare against a limited experiential baseline.

For example, using BPD as a rarer example than ADHD, a family practice physician or general clinical psychologist provided with the DSM diagnostic criteria for BPD is unlikely to have much experience with the disorder in a normal population of family practice patients.

Consequently, without experience with the type of behaviors that represent several standard deviations from the normal population, any relative outlier from a population clustered at the mean may lead to overdiagnosis due to oversensitivity to the diagnostic criteria in light of clinical inexperience with the disorder. In contrast, a psychiatrist or psychologist with prior material exposure to BPD patients would be better able to distinguish clinically significant symptoms from those that are not clinically significant. Such a clinician may also have training in assessments available to support a clinical diagnosis, such as the Minnesota Multiphasic Personality Inventory (MMPI), to support their experientially refined diagnosis. Further, comorbidities complicate diagnosis that may lead to misdiagnosis. Similarly, the existence of extensive longitudinal studies on stimulant and non-stimulate treatment paradigms is limited and long-term adverse effects of these treatments, while in some cases observed for over 60 years, are not optimally characterized in the literature reviewed. These are but a few of the legitimate concerns regarding ADHD as a disorder raised by its critics. Finally, due to comorbidities, underdiagnosis due to misdiagnosis of ADHD for other disorders is also a major concern to the diagnosis and treatment community that can benefit from RDoC informed improved differential diagnosis (Abdelnour et al., 2022).

Biological Markers of ADHD and Endophenotypes to Inform Diagnosis and Treatment. Based on literature reviewed, ADHD is a discrete, but dynamic and relational psychiatric disorder. There is substantial literature characterizing its biological basis and genetic etiology, compelling literature regarding its deviation from the norm of biology and behavior and extensive empirical evidence of its onset, progression, and treatment outcomes (Abdelnour et al, 2022; Hayman & Fernandez, 2018). However, diagnostic criteria may indeed be too subjective to differentiate it sufficiently from baseline norms, particularly as to adults, to avoid potential

overdiagnosis (Taylor et al., 2022). There is a need for both objective diagnostic criteria and finer stratification of its classification (Taylor et al., 2022). For example, Gupta et al. (2011) developed a classification system based on tests for ADHD in children. Pliszka (2006) suggested prophetic subtyping of ADHD based on comorbidity in anticipation of the DSM-V.

Biological markers, including candidate endophenotypes, have thus far failed to consistently inform differential diagnosis (Abdelnour et al., 2022; Gagnon et al., 2022). However, additional diagnostic metrics requiring functional impairment for diagnosis may miss the point of the RDoC informed biological basis and etiology of ADHD, and suggests that it be considered a condition or syndrome (consistent with the evolution of the DSM) rather than a disorder so as to not exclude those individuals who have masked its impairment with successful coping mechanisms, but nonetheless biologically present the condition (Gagnon et al., 2022). This is an RDoC informed perspective. Endophenotypes do not look for fine distinctions but represent markers of behavioral liability, such as impulsivity, that present across a spectrum of DSM disorders, such as ADHD.

Autism Spectrum Disorder (ASD)

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by (a) deficits in social communication, (b) deficits in social interaction, and (c) restricted or repetitive behavior or interests (Aishworiya et al., 2022; American Psychiatric Association, 2022; Guo et al., 2024; Hlavata et al., 2018; Lord et al., 2018). ASD has a prevalence of about 1% - 2.2% and a heritability generally reported between 37%-90% (Aishworiya et al., 2022; American Psychiatric Association, 2022; Demetriou et al., 2019; Fang et al., 2023; Hlavata et al., 2018; IACC, 2023; Lord et al., 2018; Sandin et al., 2017; Shi et al., 2020). It occurs four to five times as often in boys as in girls (Aymerich et al., 2024; Fang et al., 2023; Kalra et al., 2023; Martin et

al., 2024). Executive function deficits, including impulsivity and deficits in BRI (disinhibition), have been implicated as key to the dysfunction of ASD (Aishworiya et al., 2022; Demetriou et al., 2019; Hlavata et al., 2018; Shi et al., 2020). Consequently, impulsivity and BRI are candidate endophenotypes for ASD and understanding their genetic correlates is of interest.

Pathophysiology of ASD. The pathophysiology of ASD includes both structural and functional impairments including hyper or hypo activation of the anterior cingulate cortex and medial pre-frontal cortex (ACC-mPFC) and insula (Guo et al, 2024). EEG, fMRI, SPECT, and PET studies have confirmed dysfunction in the left insula and ACC-mPFC and have lent support to the *early brain overgrowth theory* evidencing overgrowth of both neuronal and gray matter volume (GMV), which are both shared with schizophrenia, among others (Guo et al, 2024; Vilela et al., 2024).

Comorbidities of ASD. Consistent with the above observation that deficits in executive functions including behavioral response inhibition are common in ASD, the most common comorbid disorder with ASD is ADHD, occurring in 28%-50% of ASD patients (Aishworiya et al., 2022; Lord et al., 2018; Micai et al., 2023). Anxiety, obsessive compulsive disorder, and depression are also very common in ASD (Aishworiya et al., 2022; Aymerich et al., 2024; Lord et al., 2018; Micai et al., 2023). Schizophrenia, sleep-wake disorders, and bipolar disorder are also not uncommonly co-morbid with ASD (Aymerich et al., 2024; Micai et al., 2023).

Executive function deficiencies, including deficiencies in cognitive flexibility (implicating serotonin neurotransmitter systems and encompassing task and set shifting tested by the WCST and significantly marked by high preservative errors [PE]), as well as impulsivity (disinhibition) implicating dopamine neurotransmitter systems, derivative of structural and functional abnormalities in the PFC, are key to overall ASD dysfunction (Lage et al., 2024;

Martin et al., 2024). Consequently, impulsive aggression, linked to deficits in BRI, and consequent of dopaminergic intolerance to change in the context of compulsivity (and obsessiveness) and serotonergic social provocation, is also common in ASD, occurring in about 25-53% of patients (Aishworiya et al., 2022; Lord et al., 2018; Martin et al., 2024). This may be a key reason why oppositional defiant disorder is also a common comorbidity as impulsivity is also central to that disorder (American Psychiatric Association, 2022; Lord et al., 2018). Similarly, repetitive behaviors (compulsions) that are seminal to ASD, consistent with the previously discussed orthogonal dyad of impulsivity-compulsivity, finds related obsessions (repetitive cognitions) often leading to co-morbid obsessive-compulsive disorder (OCD) also central to higher perseverative behaviors (measured by the WCST) of certain ASD populations, particularly if the patient is ego dystonic for those compulsions, with a pooled ASD-OCD prevalence of almost 12% (Aymerich et al., 2024). Whether or not differential diagnosis between ASD and OCD is characterized by the presence of insight at least to compulsive behaviors and cognitions, this study (including via the common link of perseverative errors in the WCST) can inform any such differential diagnosis or ratify a co-morbid diagnosis. Not surprisingly, there is also considerable etiopathogenetic overlap of candidate genes (discussed next) for both ASD and OCD (Aymerich et al., 2024).

Heritability and Candidate Genes of ASD. ASD has been reported to be highly heritable, between as high as 73%-93% (Lord et al., 2018; Vilela et al., 2024). As with ADHD, ASD is polygenic and heterogenic. Genome wide association studies (GWAS) have suggested that deficiencies in excitatory and inhibitory neural mechanisms create liability for ASD via an imbalance in brain circuits (neural network systems; Martin et al., 2024; Satterstrom et al., 2020; Vilela et al., 2024). Underlying all brain circuits are genes that code for them. Over 100

susceptibility (risk) genes and alleles, each with small effect, have been reported including (Table 4) inactive histone-lysine N-methyltransferase 2E (KMT2E), proprotein convertase subtilisin/kexin type 2 (PCSK2), contactin-associated protein-like 2 coding gene (CNTNAP2), methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism, oxytocin receptor encoding gene (OXTR), forkhead box protein P2 (FOXP2), serotonin transporter genes SLC6A3 and SLC6A4, neuroligin-4, X-linked protein encoding gene (NLGN4X), glycine receptor beta (GLRB), ankyrin 3 (ANK3), eukaryotic translation elongation factor 1 alpha 2 (EEF1A2), epidermal-growth-factor like, fibronectin type III and laminin G domains (EGFLAM), zinc finger DHHC-type palmitoyltransferase 2 (ZDHHC2), AGBL carboxypeptidase 1 (AGBL1), and sorting nexin 29 (SNX29, Fang et al., 2023; Lord et al., 2018; Satterstrom et al., 2020; Vilela et al., 2024; Xia et al., 2020). These genes and alleles have effects on liability for the behavioral phenotype of ASD ranging from very small to miniscule (Satterstrom et al., 2020). Of particular interest in the context of impulsivity's (and compulsivity's) relationship with dopaminergic and serotonergic neural network systems (including excitatory and inhibitory mediation by GABA) are ASD candidate genes in those neurotransmitter systems (including aberrant mesolimbic dopamine signaling and serotonergic 5-HT and SLC6A3 genes; Martin et al., 2024). These candidate genes most notably implicate the above discussed impulsive aggression among the ASD population, supported by the efficacy of dopamine antagonists in treating impulsive aggression (and thus change intolerance) and selective serotonin reuptake inhibitors (SSRI's) in treating anxiety (related to compulsive behavior, and thus social provocation also leading to impulsive aggression) discussed below (Martin et al., 2024).

Table 4*Select Candidate Genes for ASD*

Gene/Allele	Function
CNTNAP2	Cell adhesion protein
MTHFR C677T	Folate metabolism
OXTR	Oxytocin receptor
FOXP2	Transcription factor
SLC6A4	Serotonin transporter
NLGN4X	Neurologin
GLRB	Glycine receptor
ANK3	Ankyrin protein
EEF1A2	Translation elongation factor
EGFLAM	Extracellular matrix protein
ZDHHC2	Palmitoyltransferase
AGBL1	Carboxypeptidase
SNX29	Sorting nexin

Note: Table does not list all candidate (risk) genes for ASD from the literature, only those discussed in this chapter.

Classification and Diagnosis of ASD. Diagnosis of ASD requires meeting all three DSM criterion A factors (deficits in social communication and social interaction) across multiple social contexts and at least two of four criterion B factors (restricted, repetitive patterns of behavior or interests, or activities; American Psychiatric Association, 2022). Criterion A factors

are divided into deficits in (a) social-emotional reciprocity (cannot engage in back and forth or respond in social interactions, share interests, or emotions), (b) non-verbal communication (poor at body language, eye contact, inappropriate facial expression), and (c) understanding, developing, and maintaining relationships (can't make friends or show interest in peers; American Psychiatric Association, 2022). There is also an axis of severity: level 3 (requires very substantial support), level 2 (requires substantial support) and level 1 (requires support; American Psychiatric Association, 2022; Lord et al., 2018).

Level 3 patients are extremely low functioning and typically cannot use intelligible language and are often affectively detached from others (American Psychiatric Association, 2022). They are very behaviorally inflexible and become greatly distressed, even panicked, when change is introduced or a ritualistic behavior is interrupted (American Psychiatric Association, 2022). Level 3 patients can present like the Dustin Hoffman card counting autistic savant character in the movie, *Rainman*. At the other extreme, level 1 patients can typically use language and are often highly functional but fail to effectively communicate in social settings due to social disengagement and an inability to properly read social cues and, consequently, struggle to make and keep friends (American Psychiatric Association, 2022). They struggle with task switching and organization and planning (American Psychiatric Association, 2022). A level 1 patient can present like the Diane Kruger character, Sonya, a detective with Asperger's type ASD in the US TV series, *The Bridge*. With the DSM-5, Asperger's disorder, pervasive developmental disorder not otherwise specified, and autistic disorder were combined into one diagnosis of ASD leading to an increase in diagnosis and prevalence (American Psychiatric Association, 2022; Hlavata et al., 2018; Lord et al., 2018). The use of artificial intelligence

methods, including machine learning and deep learning, for classification of ASD is discussed later in this chapter in the section discussing neurocomputational methods.

Current Treatment Paradigms for ASD. Current treatments for ASD include physiotherapy, nutritional interventions, behavioral interventions (including occupational therapy), and psychopharmacological interventions (Kalra et al. 2023; Lord et al., 2018). Behavioral interventions are the first line and most common treatment modalities (Aishworiya et al., 2022). These include parent mediated behavioral interventions and so called naturalistic developmental behavioral interventions (Lord et al., 2018; Wergeland et al., 2022). The latter is the most common, particularly applied behavior analysis (ABA; Lord et al., 2018; Wergeland et al., 2022). For high functioning patients (Level 1) behavioral interventions focus on improving social skills although there is a dearth across all levels for treatment modalities targeted at impulsive aggression in ASD patients (Aishworiya et al., 2022; Lord et al., 2018).

Psychopharmacological interventions tend to focus on ASD comorbidities rather than ASD itself although they also address DSM agnostic symptoms, including impulsivity (and compulsivity or its related anxiety; Aishworiya et al., 2022; Kalra et al., 2023). These include risperidone (dopamine receptor antagonist) and aripiprazole (dopamine receptor partial agonist/antagonists; atypical second generation antipsychotics also used for schizophrenia discussed below) to quiesce impulsive aggression and irritability and atomoxetine and methylphenidate to address ADHD comorbidity (Aishworiya et al., 2022; Kalra et al., 2023; Lord et al., 2018; Martin et al., 2024). Other drugs include lovastatin, cannabidiol, oxytocin, metformin, arbaclofen, bumetanide, and trofnetide (Aishworiya et al., 2022). Selective serotonin reuptake inhibitors (SSRIs), for example, address comorbid anxiety (Aishworiya et al., 2022). Intranasal oxytocin has also had both behavioral and cognitive efficacy (Kalra et al., 2023).

Schizophrenia

Schizophrenia is a severe neurodevelopmental disorder characterized by (a) positive symptoms of psychotic delusions (primarily paranoid, grandiose, or somatic), sensory hallucinations (primarily auditory, but also visual), and disorganized thinking, speech, and behavior, (b) negative symptoms of apathy and loss or lack of affect; alogia, avolition, demotivation, and social withdrawal; and anhedonia (loss of pleasure); and (c) cognitive distortions (thought disorder of memory, attention, and executive functions) implicating the default mode network (DMN; involving the anterior cingulate cortex [ACC], posterior cingulate cortex [PCC], and medial prefrontal cortex [mPFC]), and emotional dysregulation (depression and manic symptoms; American Psychiatric Association, 2022; Correll & Schooler, 2020; Crawford & Go, 2022; Rigby & Alexander, 2008; McCutcheon et al., 2020; Os & Kaupr, 2009; Sabbah & Northoff, 2024; Walker & Tessener, 2008). Cognitive distortions lead to negative symptoms, but positive symptoms and emotional dysregulation occur independently (Os & Kapur, 2009). The Positive and Negative Syndrome Scale (PANSS) provides five symptomatic factors that broadly capture schizophrenia symptomology, namely, positive, negative, disorganized, excited, and depressed (McCutcheon et al., 2023). Schizophrenia affects about 1% of the population and may be the most debilitating form of psychosis (American Psychiatric Association, 2022; Crawford & Go, 2022; McCutcheon et al., 2020; Rigby & Alexander, 2008; Walker & Tessener, 2008; Weinberger & Harrison, 2011). Patients with schizophrenia exhibit deficits in BRI as bad or worse as those with impulse control disorders (Hoptman et al., 2018). Consequently, BRI is a suitable candidate endophenotype for schizophrenia.

Etiology of Schizophrenia. There are many theories regarding the etiology of schizophrenia. These include neurodevelopmental theories focused on enlargement of the

ventricles (as measured via structural MRI) and grey and white matter density (as measured by diffusion tensor imaging [DTI] and structural MRI), maternal health, in-utero brain injury, or and fetal development (American Psychiatric Association, 2022; Fatemi & Folsom, 2009; Howes et al., 2023; McCutcheon et al., 2020; McGrath & Murray, 2011). Other theories include the stress-vulnerability model, psychodynamic theories, psychosocial theories, including double-bind theory; diathesis-stress models, environmental liability theories, including cannabis use; and neurobiological theories, including visual tracking (American Psychiatric Association, 2022; Crawford & Go, 2022; McCutcheon et al., 2020; McGrath & Murray, 2011; Rigby & Alexander, 2008; Os & Kaupr, 2009; Walker & Tessner, 2008). More recently, evolutionary theory has been used to posit schizophrenia's etiology (Lesk, 2023), neuroinflammatory effects in white matter and metabolic stress (Helaly & Ghorab, 2023), as well as pathological perturbation of the topological architecture of global neural networks (Gao et al., 2023). Most current perspectives combine gene-environmental interactions and subscribe to multiple theories, such as the neurodevelopmental theory in light of genetic liability (the polygenic threshold model; Crawford & Go, 2022; McCutcheon et al., 2020). One such theory, discussed next, is particularly relevant and well-studied in the literature.

Dopamine Hypothesis of Schizophrenia. One key theory of the etiology of schizophrenia that this study subscribed to is the dopamine (DA) hypothesis of schizophrenia (DHS). The DHS posits that either (a) overstimulation (over-sensitivity) of dopamine receptors or (b) over-transmission of dopamine (including under-suppression or de-suppression of dopamine), resulting in excessive post-synaptic dopamine tone, imparts etiological liability for schizophrenia (Abi-Dargham & Grace, 2011; Howes & Kapur, 2009; Kendler & Schaffner, 2011; Lesk, 2023; McCutcheon et al., 2023; McCutcheon et al., 2020; Peng et al., 2024; Stahl, 2011; van

Hooijdonk et al., 2023). These versions of the hypothesis implicate both mesolimbic and mesocortical DA neural network systems (as well as the substantia nigra [SN]) involved in DA expression (Howes & Kapur, 2009; Kendler & Schaffner, 2011; McCutcheon et al., 2023; McCutcheon et al. 2020; Stahl, 2011; van Hooijdonk et al., 2023). The DHS particularly implicates psychosis in schizophrenia, but also implicates broader aspects, including impulsivity, which is highly correlated with DA neural network systems (Howes & Kapur, 2009; Os & Kapur, 2009; Stahl, 2011). Many studies, such as fMRI or qEEG studies using laboratory behavioral measures, that investigate the DHS also touch on similar biological markers for deficits in behavioral response inhibition (Howes & Kapur, 2009; Os & Kapur, 2009). Similarly, many of the same brain regions implicated in schizophrenia from fMRI studies, including the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), and medial and ventromedial prefrontal cortex (VMPFC), are also implicated in impulsivity and behavioral response inhibition as discussed elsewhere in this chapter (Dattola et al., 2020; Fatemi & Folsom, 2009; Peng et al., 2024; Stahl, 2011). The DHS also implicates numerous genetic correlates. Genetic liability of schizophrenia is discussed next.

Heritability and Candidate Genes of Schizophrenia. Like with ADHD and ASD, the heritability of schizophrenia is extremely high, between 50% and 80% (Hilker et al., 2018; Kuehn, 2009; McCutcheon et al., 2020; Nakamura & Takata, 2023; Nestler et al., 2009; O'Donovan & Owen, 2011; Os & Kapur, 2009; Roofeh et al., 2013; Szesko et al., 2008). Because impulsivity in those with schizophrenia can result in harm of self or others, often leading to incarceration or involuntary commitment, as an endophenotype of schizophrenia, its genetic origins are of particular interest (Hoptman et al., 2018). Like ADHD and ASD, schizophrenia is also polygenic and heterogenic (McCutcheon et al., 2020; Nakamura & Takata,

2023). Gene mapping, gene linkage, gene association, candidate gene, and genome wide association studies (GWAS) have produced over 100 candidate genes for schizophrenia (McCutcheon et al., 2020; Nakamura & Takata, 2023; Riley & Kendler, 2011; Roofeh et al., 2013).

Risk (susceptibility) genes (including allelic SNPs and CNVs) include disrupted in schizophrenia 1 and 2 (DISC1/DISC2; Fatemi & Folsom, 2009; Kuehn, 2009; Nestler et al., 2009; O'Donovan & Owen, 2011; Szesko et al., 2008), rs140365013 (a major histocompatibility region (MHC) pleiotropic SNP; Nakamura & Takata, 2023), dystrobrevin binding protein 1 (DTNBP1), neuregulin 1 (NRG1), D-amino acid oxidase activator (DAOA), and regulator of G protein signaling 4 (RGS4; Fatemi & Folsom, 2009; Nestler et al., 2009; Riley & Kendler, 2011); zinc finger protein 804A (ZNF804A; Mossner et al., 2012), cannabinoid receptor type 1 (CB1; Dalton et al., 2011), dopamine 2 (DRD2) and 3 (DRD3) receptors (Fatemi & Folsom, 2009; Kendler & Schaffner, 2011; O'Donovan & Owen, 2011), serotonin 2A (5-HT2A; O'Donovan & Owen, 2011; Olajossy-Hilkesberger et al., 2011), catechol-O-methyl transferase (COMT; Kendler & Schaffner, 2011; Riley & Kendler, 2011), and brain-derived neurotrophic factor (BDNF C-281A; Suchanek et al., 2012). Table 5 summarizes these genes. More comprehensive lists can be found in Fatemi and Folsom (2009), Nakamura and Takata (2023), Roofeh et al. (2013), and Stahl (2011). Again, each is of small effect at best (O'Donovan & Owen, 2011).

Table 5*Select Candidate Genes for Schizophrenia*

Gene/Allele	Function
DISC1	Neural development
DIS2	Neural development
DTNBP1	Dystrobrevin binding
NRG1	Neuregulin signaling
ZNF804A	Transcription factor
CB1	Cannabinoid receptor
DRD2	Dopamine receptor
DRD3	Dopamine receptor
5-HT2A	Serotonin 2A receptor
COMT*	Catechol metabolism
BDNF C-281A	Neurotrophic factor

Note: Table does not list all candidate (risk) genes for schizophrenia from the literature, only those discussed in this chapter.

*Shared select candidate gene with borderline personality disorder.

Classification and Diagnosis of Schizophrenia. Diagnosis of schizophrenia requires a patient to exhibit, for a significant period of time during a month, (a) at least one of hallucinations (disorder or perception comprising sensory experiences without a sensory stimulus), delusions (thought content disorder comprising beliefs contrary to reality and lack of reality testing), and disorganized speech (thought disorder comprising fragmentation, derailment,

or incoherence) plus another of the above three symptoms or (b) either grossly disorganized or catatonic behavior or (c) negative symptoms (diminished emotional expression, blunted affect, impoverished speech, anhedonia, and social withdrawal; American Psychiatric Association, 2022; Rigby & Alexander, 2008; Stahl, 2011). Consequently, one patient can be diagnosed with schizophrenia with only one of hallucinations, delusions, or disorganized speech, for example. Another patient can be diagnosed with schizophrenia without negative symptoms if they present with hallucinations and delusions, for another example. Yet another patient can be diagnosed with schizophrenia with just delusions and disorganized speech, as a further example.

The most common negative symptoms are often characterized as the six A's (alogia [poverty of speech or speech content], affective flattening [reduced emotional expression], anhedonia [inability to experience pleasure], asociality [lack of interest in social contacts], avolition [lack of motivation], and apathy [lack of interest in anything]; Arango & Carpenter, 2011; Stahl, 2011). Criterion B requires a severely deficient ability to function or engage in self-care, often a key behavioral marker of schizophrenia (American Psychiatric Association, 2022). As with ADHD, ASD, and BPD, schizophrenia patients also typically present with significant deficits in behavioral response inhibition (American Psychiatric Association, 2022).

Schizophreniform disorder is typically the diagnosis for patients who present with the above symptoms for less than six months, as schizophrenia requires greater than six-month persistence in symptoms, including dampened prodromal presentation of symptoms following six months (American Psychiatric Association, 2022). The use of artificial intelligence methods, including machine learning and deep learning, for classification of schizophrenia is discussed later in this chapter in the section discussing neurocomputational methods.

Current Treatment Paradigms for Schizophrenia. Antipsychotic drugs continue to represent first line treatment modalities and target dopaminergic D2 receptors (implicating the DHS discussed above; Crawford & Go, 2022; McCutcheon et al., 2023; McCutcheon et al., 2020; Os & Kapur, 2009; Peng et al., 2024; Stahl, 2011; Waddington et al., 2011). So called typical first generation antipsychotics include haloperidol, fluphenazine, loxapine, perphenazine, and chlorpromazine (Thorazine; Crawford & Go, 2022; Os & Kapur, 2009; Stahl, 2011). First generation antipsychotics often result in Tardive Dyskinesia (a motor disorder; Crawford & Go, 2022; Os & Kapur, 2009; Stahl, 2011). Atypical second-generation antipsychotics, including clozapine, risperidone, olanzapine, quetiapine, ziprasidone, sertindole, ziprasidone, brexpiprazole, cariprazine, lurasidone, lumateperone, and aripiprazole have less severe motor side effects, although they have other deleterious side effects, including weight gain and extrapyramidal symptoms (Crawford & Go, 2022; McCutcheon et al., 2020; Os & Kapur, 2009; Peng et al., 2024; Stahl, 2011; Waddington et al., 2011). Trace amine-associated receptor 1 (TAAR1) agonists (such as SEP-363856 in clinical trials as of 2025) that reduce dopamine tone (via TAAR1 and 5-HT1A agonism) also show promise to reduce psychosis and also potentially improve cognitive deficits and excitatory and inhibitory neurotransmitter balance (McCutcheon et al., 2023; Peng et al., 2024; Sumitomo, 2024). The above medications bring a vast majority of patients into remission, but patient non-compliance due to negative symptoms, demotivating side effects of antipsychotic medications, and ego syntonia (anosognosia) contribute to relapse without community based adjunct therapy (Os & Kapur, 2009). Consequently, absent chronic psychopharmacological intervention and community team-based intervention to provide support for medication compliance, prognosis for most schizophrenia patients is extremely poor (Lieberman et al., 2020).

Relationship Between Schizophrenia and Borderline Personality Disorder.

Schizophrenia symptomatically overlaps with, and is phylogenetically and developmentally related to, borderline personality disorder (BPD), discussed next (Zandersen & Parnas, 2020). In addition to impulsivity (disinhibition), including impulsive aggression, key overlapping symptoms between schizophrenia and BPD include interpersonal constitutional hypersensitivity/distress tolerance, delusions, hallucinations, identity disturbance, self-disorder, identity diffusion, and cognitive distortions (Bonfils & Lysaker, 2020; Kingdon et al., 2010; Zanderson & Parnas, 2020). Depersonalization and derealization and somatic complaints often seen in borderline personality disorder may also progress to severe delusional levels in schizophrenia patients (American Psychiatric Association, 2022). Indeed, many BPD patient behavioral phenotypes would meet the criteria for schizophrenia (Kingdon et al., 2010; Zandersen & Parnas, 2020). Psychotic features in schizophrenia and BPD are similar to such an extent that psychosis is transdiagnostic between the two, suggesting not only common neural correlates, but lending support to some level of merging between the two, at least as to magnitude and character of certain symptoms (Biancalani et al., 2023; Pelizza et al., 2024).

Some have argued that schizophrenia and BPD are virtually indistinguishable in certain behavioral phenotypes, while others suggest BPD is indistinguishable from schizotypal personality disorder or at least from the schizophrenia spectrum disorders generally (American Psychiatric Association, 2022; Cavelti et al., 2019; Kety, 1985; Spitzer et al., 1979; Zandersen & Parnas, 2020). Meehl (1989), for example, posited that most borderlines are actually schizotypes. This suggests that, perhaps, BPD falls on the schizophrenia spectrum continuum, precedent to schizotypal personality disorder, which is precedent to schizophreniform disorder, which is precedent to schizophrenia (Kety, 1985; Zandersen & Parnas, 2020). For example, if transient

delusions in a BPD patient become chronic and more implausible, and hallucinations become common or more auditory, and a patient is fully ego syntonic, they may more likely meet the criteria for schizophrenia. In that sense, BPD may be described in certain behavioral phenotypes as latent schizophrenia or borderline schizophrenia, consistent with Adolf Stern's original construct of BPD (Bleuler, 1950; Kety et al., 1968; Spitzer et al., 1979; Stern, 1938; Zanarini & Fankenburg, 2007; Zandersen & Parnas, 2020). Because of the plural symptomatic overlap between schizophrenia and BPD, if operational embodiments of impulsivity between the two can be distinguished by the findings of this study described in Chapter 4 and suggested future research in Chapter 5, it may help improve differential diagnosis between them. BPD is discussed next.

Borderline Personality Disorder

Borderline personality disorder (BPD) is a severe Axis II Cluster B (dramatic-erratic) personality disorder characterized by cognitive distortions (thinking), emotional dysregulation (feeling), and impulsive behavior (acting, American Psychiatric Association, 2013; American Psychological Association, 2022; Gunderson et al., 2018; Kernberg & Michels, 2009; Koudys et al., 2018; Kulacaoglu & Kose, 2019; Lieb et al., 2004; Lombardo et al., 2023; Mendez-Miller et al., 2022; S. G. Miller, personal communication, May 2020; Paris, 2020; Wibbelink et al., 2022). It is arguably the most complex behavioral phenotype of the four discussed in detail in this study and, along with schizophrenia, the most severe. It occurs in between 2% to 6% of the population and is the most common personality disorder found in clinical settings including 10%-28% of outpatient, 20% of inpatient, 10-15% of emergency room admissions, and 30% of forensic populations (Bozzatello et al., 2021; Gunderson, 2011; Gunderson et al., 2018; Kernberg & Michels, 2009; Kulacaoglu & Kose, 2019; Koudys et al, 2018; Lieb et al., 2004; Mendez-Miller

et al., 2022; Nemeh & Khandai, 2024; Paris, 2020; Pascual et al., 2023; Sajjadi et al., 2021; Sansone & Sansone 2009; Sansone & Sansone, 2012; Sperry, 2016; Vogt & Norman, 2022; Wibbelink et al., 2022). BPD is the most researched and difficult to treat of all personality disorders (Gunderson et al., 2018; Herpertz et al., 2007; Kernberg & Michels, 2009; Nemeh & Khandai, 2024; Paris, 2020; Sperry, 2016). Indeed, the number of research articles on BPD found for this study were an order of magnitude higher than those found for the next highest personality disorder.

Although BPD is often considered primarily a personality disorder common in women (75%-80% of clinical populations of BPD patients are women), when these statistics are reported, they refer to clinical rather than general populations and thus are misleading with respect to prevalence in the general population where the distribution between male and female is less significant (Gunderson, 2011; Kulacagolu & Kose, 2019; Paris, 2020). Reasons for this discrepancy include higher ego syntonia in male patients, lower incidence of males seeking treatment, and higher comorbidity of narcissistic personality disorder and antisocial personality disorder among male patients (Gunderson, 2011; Kulacagolu & Kose, 2019; Paris, 2020).

Impulsivity's and BRI's Role in BPD. As discussed previously in this chapter, impulsivity is a hallmark of BPD in both the DSM-5-TR proper and in the DSM-5-TR alternative model for personality disorders and presents a distinct trait dimension from cognitive distortions and emotional dysregulation (American Psychiatric Association, 2022; Bozzatello et al., 2022; Kulacaoglu & Kose, 2019; Links et al., 1999; Lombardo et al., 2023; Mendez-Miller et al., 2022; Mungo et al., 2020; Paris, 2020; Riffer et al., 2019; Ruocco et al., 2021; Sperry, 2016; Tragesser et al., 2010; Vanwoerden & Stepp, 2022; Waite et al., 2024; Wojciechowski, 2021). The ICD-10 has also divided BPD into two subtypes, including impulsive subtype (Riffer

et al., 2019). Impulsivity/disinhibition is one of two BPD features that are most researched in the BPD literature (Koudys et al., 2018; Tragesser et al., 2010; Waite et al., 2024). High levels of impulsivity are the most significant prognostic indicators among BPD clinical samples, particularly with respect to suicide (Bozzatello et al., 2022; Mendez-Miller et al., 2022; Mungo et al., 2020; Paris, 2020; Riffer et al., 2019; Ruocco et al., 2021; Waite et al., 2024; Wibbelink et al., 2022). As many as 80% of BPD patients (i.e., from the clinical population) attempt suicide and 10% succeed, a rate 50 times that of those who attempt suicide in the general population (Bozzatello et al., 2021; Lieb et al., 2004; Mendez-Miller et al., 2022; Mungo et al., 2020; Riffer et al., 2019).

Impulsivity, manifested as a deficit in BRI (disinhibition), is often an operational consequence of severe emotional dysregulation incited by cognitive distortions in combination with environmental stressors and triggers and includes impulsive aggression and borderline rage (Gunderson et al., 2018; Koudys et al., 2018; Kulacaoglu & Kose, 2019; Lombardo et al., 2023; Paris, 2020; Sperry, 2016; Waite et al., 2024; Wojciechowski, 2021). While impulsive aggression and borderline rage are manifestations of instrumental behavioral reactions to stressors or cognitions, in BPD they are compounded by cognitive rumination of anger, stress, interpersonal offense, anxiety, and depression that contribute to hypermentalization of others (Oliva et al., 2023; Mitolo et al., 2024). In that sense, borderline rage can be described as a hypermentalization enabled hyperbolic instrumental and reactive form of the impulsive aggression also seen in ASD and schizophrenia. Indeed, the dysfunctional cognitive strategy of anger rumination (brooding) may be the greatest contributor to negative hypermentalization of others in BPD and, thus, to emotional dysregulation that manifests as impulsive aggression and borderline rage (Oliva et al., 2023). Impulsive aggression and its hyperbolic embodiment in

borderline rage (or even more extreme annihilating borderline rage) often leads to intimate (attachment) partner domestic violence (IPV), whether physical or psychological (Guzmán et al., 2024; Leucci et al., 2024). Disinhibition (deficits in BRI) are particularly linked to impulsive aggression (Guzmán et al., 2024). Further, among the numerous trait dimensions, features, and symptoms of BPD, impulsivity and deficits in BRI (disinhibition) are the most stable and present the most consistent biological correlates, providing opportunity to understand BPD's neurobiological etiology and treatment (Gunderson et al., 2018; Koudys et al., 2018; Paris, 2020; Riffer et al., 2019; Tragesser et al., 2010; Waite et al., 2024). Consequently, impulsive aggression, stress potentiated impulsivity, and deficits in BRI are all among putative endophenotypes in the literature for BPD (Bassier Nia et al., 2018).

The above does not suggest, however, that impulsivity or certain facets of impulsivity (or BRI) are the best behavioral targets for differential diagnosis, precisely because impulsivity is so common across so many DSM disorders. In BPD, of the trait dimensions, cognitive distortions may be the best differentiating domain (see, however, the schizophrenia discussion above regarding trait dimensions of schizophrenia and BPD and possibly discriminating impulsivity between the two) although they may not be present in all cases, since they are far more rare than either emotional dysregulation or impulsivity domains (Paris, 2020). However, this study may help improve impulsivity's (and BRI's) role as a diagnostic differentiator. After all, the extreme aggression and so-called borderline rage (extreme hyperbolic instrumental reactive impulsive aggression and its hyper-extreme counterpart annihilating borderline rage) presents rather uniquely in BPD patient populations and may be a key differential diagnostic behavioral marker with anger rumination as a risk factor (Guzmán et al., 2024; Kanwal & Kazmi, 2022; Oliva et al., 2023; Sansone & Sansone, 2012; Wojciechowski, 2021).

Indeed, deficiencies in BRI can present opportunity for differential diagnosis of BPD. For example, deficiencies in BRI as measured by go/no-go and the BIS-11, are uniquely active in BPD patient samples when environmental triggers and stressors are present, while deficits in BRI in ADHD patient samples are not dependent on stressors (Gunderson et al., 2018; Waite et al., 2024). Further, impulsivity and deficits in BRI as a behavioral target for differential diagnosis also implicates treatment prognosis. Impulsivity may be the most treatable symptom of BPD (Gunderson et al., 2018). Given its central role in the negative impact and prognosis of the disorder, improved understanding of its operational facets for etiology and differential diagnosis as informed by this study would contribute to the BPD literature.

At any rate, some in the BPD research and treatment communities suggest all three trait dimensions of BPD should be present for a positive diagnosis, which would be an argument against alternative names suggested by others for the disorder, such as emotional dysregulation disorder (Koudys et al., 2018; Paris, 2020) or emotionally unstable personality disorder as it is officially called under the ICD-10. This is arguably a more balanced perspective than that promoted by the various schools of thought on whether BPD is primarily a disorder of cognitive distortions (Kernberg & Michels, 2009), emotional dysregulation (Linehan, 1993), or impulse control (Zanarini, 1993). Each of those perspectives arguably suggests that the primary feature (e.g., emotional dysregulation) causes or is far more important than the other features. But those perspectives fail to take an NDST (discussed early in this chapter) holistic view of agency and feedback and bidirectional interactions among features. One feature may foment another, which may foment yet another, which may provide feedback to the first feature and exacerbate it. Consequently, arguably, treating BPD as a primarily an emotional dysregulation disorder, or primarily a cognitive distortion disorder, or primarily an impulse control disorder, discounts or

even dismisses the other two features and ignores the far more dynamic and complex interaction among all three. With respect to treatment, the concept of safety (not to mention interpersonal salience) of the patient and that of others suggests to first target operational embodiments of the afflicted, dysfunctional impulsive behavior (acting), which is shared with comorbid disorders. A more detailed review of the many schools of BPD's pathogenesis can be found in Koudys et al. (2018) and Zanarini and Frankenburg (2007).

Comorbidities of BPD. 85% of BPD patients have comorbid psychiatric disorders (Kulacaoglu & Kose, 2019; Mendez-Miller et al., 2022). Anxiety disorders (including panic disorder) and post-traumatic stress disorder (PTSD) are most common, present in as many as 88% of BPD patients (Ajinkya et al., 2021; Bozzatello et al., 2021; Gunderson et al., 2018; Jørgensen et al., 2024; Kulacaoglu & Kose, 2019; Nemeh & Khandai, 2024; Pascual et al., 2023; Sperry, 2016; Vogt & Norman, 2022). Complex post-traumatic stress disorder (CPTSD) is also common, though not a distinct disorder from PTSD in the DSM-5-TR, although it is separately listed in the ICD-11 (Atkinson et al., 2024; Gutierrez & Tucker, 2024). CPTSD is a more chronic form of PTSD often tied to childhood trauma (adverse childhood experiences [ACEs]; Atkinson et al., 2024). CPTSD shares with BPD not only impulsivity (impulsivity has also been argued to be a distinguishing characteristic between BPD and CPTSD), but also, emotional dysregulation, identity dissociation (although dissociation is seen more in BPD than CPTSD), identity diffusion, suicidal ideation, and unstable relationships (Atkinson et al., 2024). Consequently, CPTSD has been suggested to be a subtype of BPD (Atkinson et al., 2024). However, BPD has also been suggested to be a form of CPTSD, although this has been shown to be a misleading oversimplification, since a significant portion of the BPD population (29%-60%) lacks a trauma history or adverse childhood experiences (ACEs) and the presence of either does not predict

development of BPD (Atkinson et al., 2024; Paris, 2020). Notwithstanding these opposing perspectives, CPTSD both overlaps with BPD and is distinct from it (Atkinson et al., 2024; Gutierrez & Tucker, 2024; Paris, 2020; Riffer et al., 2019). Supporting this distinction, standard PTSD therapeutic treatments are often contraindicated in BPD populations, particularly for those BPD patients that are suicidal (Choi-Kain et al., 2017). With that context, CPTSD and BPD have a combined prevalence of 20%-53% (Jørgensen et al., 2024).

ADHD, which shares marked impulsivity with BPD, particularly motor impulsivity, is also very common in the BPD population (Jørgensen et al., 2024; Linhartova et al., 2019; Pascual et al., 2023). Adult ADHD is often reported in 20% of BPD adult clinical samples and 60% of adult BPD clinical samples report childhood ADHD (Bozzatello et al., 2021; Gunderson et al., 2018; Jørgensen et al., 2024; Kulacaoglu & Kose, 2019; Riffer et al., 2019). As discussed in the previous section, schizophrenia and BPD share common key genetic correlates, echoing the original construct of BPD by Adolf Stern as a disorder on the border between neurosis and psychosis and BPD's potentially precursive prodromal relationship to schizophrenia (Stern, 1938; Wit et al., 2017). Almost 40% of BPD patients have comorbid psychotic disorders, including schizophrenia, and 17-25% of schizophrenia patients meet the diagnostic criteria for BPD (Jørgensen et al., 2024). Delusions occur in 15-30% of BPD patients and hallucinations occur in 43% (Jørgensen et al., 2024; Pelizza et al., 2024). Psychotic symptoms in BPD differ from those in schizophrenia in that auditory hallucinations in BPD load more heavily (ranging from 25-50% in clinical samples) than visual hallucinations do, although differences in auditory hallucinations in BPD and schizophrenia are evasive to identify (Biancalani et al., 2023). Nonetheless, early psychosis in the lifespan has been considered a suitable marker for early

diagnosis of BPD, particularly since marked psychosis is predictive of more severe forms of BPD with poorer prognosis (Biancalani et al., 2023; Pelizza et al., 2024).

Other Axis I comorbidities include bipolar disorder (also a common misdiagnosis), major depressive disorder (as high as 83% in BPD patient samples), dysthymic disorder, and dissociative disorders (Bozzatello et al., 2021; Gunderson et al., 2018; Jørgensen et al., 2024; Kulacaoglu & Kose, 2019; Lieb et al., 2004; Paris, 2020; Pascual et al., 2023; Sperry, 2016). With respect to dissociation, its role in BPD can be quite significant and differentiating although not often the focus of empirical research (Mazinan et al., 2024). For example, impulsive sex in BPD patients with a traumatic childhood and adverse childhood experiences (ACEs) can co-occur with dissociation, detachment (depersonalization and derealization), and/or conversion (and somatization), which are also found in PTSD/CPTSD (Mazinan et al., 2024).

With respect to Axis II disorders, as many as 60% of BPD patients have comorbid severe personality disorders, particularly histrionic, narcissistic, antisocial, avoidant, obsessive compulsive, dependent, and, as noted in the previous section, schizotypal personality disorders (Bozzatello et al., 2022; Jørgensen et al., 2024; Kernberg & Michels, 2009; Paris, 2020; Sperry, 2016). Narcissistic personality disorder (NPD; pathological narcissism, since functional narcissism is not always a disorder) is often comorbid with BPD with overlapping symptoms including impulsivity, impulsive aggression, and ego syntonia (poor insight into one's illness; Cain et al., 2024). After all, Kernberg's psychoanalytic object relations theory grounded concept of borderline personality organization (BPO) included both borderline and narcissistic adaptations, encompassing the most severe personality disorders (Cain et al., 2024; Kernberg, 2004; Summers, 2024).

Malignant narcissism, a more extreme form of pathological narcissism sometimes comorbid with BPD, and sometimes (in more extreme presentations often accompanied by annihilating borderline rage) also overlaps with antisocial personality disorder (APD), sadism, and psychopathy and the so-called dark triad of Machiavellianism, psychopathy, and narcissism (Cain et al., 2024; Miller et al., 2010; Lenzenweger et al. 2018; Paulhus & Williams, 2002). This subset of a subset of BPD patients are the most difficult to treat (assuming they seek or agree to treatment at all), have the poorest prognosis, and employ the most severe forms of impulsivity and impulsive aggression (Cain et al., 2024; Lenzenweger et al., 2018). Yet (being founded on dysfunctional objection relations to others and imbued with externalizing extreme impulsive aggression and annihilating borderline rage) this small subclass of BPD can be the most dangerous and harmful to others, both via physical, sometimes extreme, violence and extreme psychological abuse as a product of that extreme impulsive aggression and annihilating borderline rage (Cain et al., 2024; Lenzenweger et al., 2018). BPD patients comorbid with NPD and malignant narcissism and the other above traits often present the most extreme fragmentation of self, ego syntonia, impulsive aggression (annihilating borderline rage), what can arguably be described as disaffectation (the psychoanalytic counterpart to neuropsychological alexithymia) empathy, a monolithic dysfunctional form of shallow empathy with want of functional empathy and compassion; negative primitive coping behaviors (projective identification and manipulation), and psychosis, particularly paranoid delusions, often the source of reactive impulsive aggression and violence in schizophrenia (Cain et al., 2024; Kernberg, 2004; Lenzenweger et al., 2018). For a comprehensive list of studies on comorbidities of BPD see Bozzatello et al., (2021).

Etiology of BPD. Early perspectives of BPD derived from psychoanalytic tradition. Kernberg (2004), for example, described borderline personality organization (BPO) as the most severe form of character pathology. BPO, which includes narcissistic adaptations, is a broader construct than the modern concept of BPD (Kernberg, 1984; Kernberg, 2004; Kernberg, 2018). Historically, BPD was thought to be caused by one or a combination of numerous factors. These can be divided into developmental trauma, constitutional hypersensitivity, and neurobiological/genetic factors (Trimboli & Marshall, 2020; Zanarini & Frankenburg, 2007). Developmental trauma includes childhood trauma (adverse childhood experiences [ACEs] comprising maltreatment or neglect) and an invalidating childhood environment (Lombardo et al., 2023; Trimboli & Marshall, 2020). These two sources were thought (and in some circles are still thought) to be the primary, if not exclusive, cause of BPD, each causing insecure or disorganized attachment styles (Bozzatello et al., 2021; Gunderson, 2011; Kulacaoglu & Kose, 2019; Lee et al., 2021; Mancinelli et al., 2024; Paris, 2020; Sperry, 2016; Vogt & Norman, 2022). Bozzatello et al. (2022) provides a comprehensive list of studies investigating trauma related risk factors. However, correlation is not causation and childhood trauma and an invalidating childhood is not present in a significant number, or even a majority, of the BPD clinical population and, further, most children exposed to childhood trauma do not develop BPD (Gunderson et al., 2018; Kulacaoglu & Kose, 2019; Paris, 2020; Sperry, 2016). This suggests that a childhood trauma history or ACEs are risk factors at best, albeit significant ones, a predisposition to the disorder, genetic or otherwise (Bozzatello et al., 2021; Gunderson et al., 2018; Kulacaoglu & Kose, 2019; Mendez-Miller et al., 2022; Paris, 2020; Sperry, 2016). It also suggests that different treatment modalities (discussed below) may be efficacious in different BPD patient sub-types, with trauma ACE samples responding to one type of treatment and others

to different treatments (Bozzatello et al., 2021; Trimboli & Marshall, 2020; Wibbelink et al., 2022). Constitutional hypersensitivity (thin emotional skin) is a well-documented risk factor for BPD (Paris, 2020; Trimboli & Marshall, 2020; Zanarini & Frankenburg, 2007). Anger rumination (and other forms) were discussed previously as potential risk factors as well (Oliva et al., 2023).

Neurobiological and genetic correlates are also key risk factors for BPD (Bozzatello et al., 2021; Trimboli & Marshall, 2020). Neurobiological etiology is thought to include higher cortisol levels in BPD patients and decreased volume in the hippocampus, amygdala (including hyperarousal), and medial temporal lobe (Berlin et al., 2003; Berlin et al., 2005; Gunderson, 2011; Kulacaoglu & Kose, 2019; Mitolo et al., 2024; Noor et al., 2024; Paris, 2020; Schurz et al., 2024). More specifically in the context of impulsivity in BPD, deficits in the anterior cingulate cortex (ACC), prefrontal cortex, dorsolateral prefrontal cortex (dlPFC), orbitofrontal cortex, ventro-medial prefrontal cortex (vmPFC), dorsomedial prefrontal cortex, default mode network (DMN), insula (decreased cortical thickness associated with anger rumination and impulsive anger), amygdala (decreased volume and deficits in functional connectivity tied to anger rumination and impulsive anger), and serotonergic neural network circuits, which are closely related to impulsivity and other executive function dysfunction, have been observed in BPD clinical populations (Berlin et al., 2003; Bozzatello et al., 2021; Gunderson, 2011; Gunderson et al., 2018; Kulacaoglu & Kose, 2019; Mitolo et al., 2024; Noor et al., 2024; Schurz et al., 2024; Shafie et al., 2023; Ruocco et al., 2021; Yi et al., 2024). Increased functional connectivity (FC) between DMN and limbic cortical circuits (hippocampal and parahippocampal) as determined in rs-fMRI and mapped onto BIS-11 attentional impulsiveness, but also implicating motor impulsiveness, has been found in BPD patient samples (Mitolo et al., 2024; Noor et al., 2024;

Shafie et al., 2023; Yi et al., 2024). These comprise the combination of prefronto-limbic dysfunction of BPD that is often reported in the literature that also includes gray and white matter volumetric variance (Gunderson et al., 2018; Ma et al., 2016; Mitolo et al., 2024; Noor et al., 2024; Schurz et al., 2024; Shafie et al., 2023; Yi et al., 2024). The ACC, for example, is biologically implicated in theory-of-mind (perception and understanding the distinction between self and other) and a delineated RDoC construct and is also a target of two psychodynamic/psychoanalytic treatment modalities discussed below, mentalization based psychotherapy and transference-based psychotherapy (Gunderson et al., 2018).

Heritability and Candidate Genes of BPD. As with ADHD, ASD, and schizophrenia, BPD is also highly heritable, from 40% to 70% (Bassir Nia et al., 2018; Bozzatello et al. 2021; Gunderson, 2011; Gunderson et al., 2018; Ma et al., 2016; Marceau et al., 2018; Reichborn-Kjennerud, 2010; Skoglund et al., 2021). Because impulsive behavior and deficits in BRI are central to BPD's behavioral manifestations, which can include harm of self and others, these were suitable endophenotypes for its study, including BPD's genetic origins (Bassir Nia et al., 2018; Svaldi et al., 2012). As with ADHD, ASD, and schizophrenia, BPD is also polygenic and heterogenic. Susceptibility (risk) genes include the dopaminergic system genes, including dopa decarboxylase (DDC) gene and dopamine receptor four (DRD4), including the DRD4-7R allele; and serotonin system related genes, including monoamine oxidase A (MAOA), serotonin receptor 2C (5-HT2C), tryptophan hydroxylase 2 (TPH2), and serotonin transporter (SERT) and serotonin-transporter-linked promoter region (5-HTTLPR), which again exhibit small effect on liability for the behavioral phenotype (Ma et al., 2016; Svaldi et al., 2012). Catechol o-methyltransferase (COMT) val158met polymorphism has been identified related to impulsive aggression in BPD clinical samples (Bassir Nia et al., 2018; Ma et al., 2016). Table 6

summarizes these genes. For a more comprehensive discussion of candidate genes for BPD, including gene-environment interactions, see Bassir Nia et al. (2018) and Gunderson et al. (2018).

Table 6

Select Candidate Genes for Borderline Personality Disorder

Gene/Allele	Function
DRD4-7R VNTR*	Dopamine transporter
5-HTTLPR*	Serotonin transporter
COMT**	Catechol metabolism
DDC	Dopa decarboxylase
MAOA	Monoamine oxidase
5-HT2C	Serotonin 2C receptor
TPH2	Tryptophan hydroxylase

Note: Table does not list all candidate (risk) genes for BPD from the literature, only those discussed in this chapter.

*Shared select candidate gene with ADHD

**Shared select candidate genes with schizophrenia.

As shown below, BPD occurs across at least three trait dimensions and presents with a plurality of symptoms (nine criterion dimensions) that implicate unique psychological constructs as well as at least seven characteristic coping behaviors. As described previously in this chapter, trait dimensions and symptoms themselves are highly heritable. Consequently, the total heritability of a highly heritable disorder, such as BPD, is a product of the sum of heritability of

its trait dimensions and symptomatic constructs (Gunderson et al., 2018). Studying these dimensions and constructs, such as impulsivity and BRI, whether via top-down process of decomposition or a bottom-up process of composition may improve the etiological inquiry and differential diagnosis of BPD (Paris, 2020).

Classification and Diagnosis of BPD. Diagnosis of borderline personality disorder starts with the cluster of behaviors associated with the cluster B personality disorders including a pervasive pattern of unstable relationships, self-image, and emotional affect that is marked by impulsivity (American Psychiatric Association, 2022). To meet the DSM criterion, a patient must present with five or more of the following nine symptoms: (a) frantic efforts to avoid real or imagined abandonment (interpersonal sensitivity), (b) a pattern of unstable and intense relationships that cycle between periods of idealization and devaluation (splitting), (c) an unstable sense of self or self-image (self-disorder or identity diffusion), (d) impulsive behavior in at least two self-harmful areas, such as substance abuse or sex, (e) suicidal behaviors or internalizing self-harm, such as cutting, (f) emotional instability resulting from hyperbolic mood states, including intense irritability, dysphoria, and anxiety that can last from hours to days (constitutional hypersensitivity), (g) chronic feelings of emptiness (loss of self), (h) contextually inappropriate and uncontrollable extreme anger or rage (externalizing instrumental reactive impulsive anger and aggression or borderline rage), (i) and transient paranoid ideation or severe dissociation triggered by stressors (affective phase shifts; American Psychiatric Association, 2022; Bozzatello et al., 2021; Gunderson, 2011; Koudys et al., 2018; Kulacaoglu & Koss, 2019; Mendez-Miller et al., 2022; Nemeh & Khandai, 2024; Paris, 2020). Using the three dimensions above (thinking, feeling, acting), which were described to this author by the late Dr. Steven G. Miller, a former Harvard Medical School colleague of BPD pioneering researcher John

Gunderson (S. G. Miller, personal communication, May 2020), three of the criteria ([c], [g], [i]) are associated with cognitive distortions (thinking); three ([a], [b], [f]) are associated with emotional dysregulation (including interpersonal sensitivity; feeling); and three ([d], [e], [h]) are associated with impulsivity (acting; Mendez-Miller et al., 2022).

Borderline patients who are high functioning and/or ego syntonic (i.e., they have no insight into their illness) for the disorder are less likely to present with suicidal ideation or behaviors or *cry for help* and seek medical or psychiatric treatment, than an ego dystonic (i.e., the patient has insight that something is very wrong with them) presentation commonly associated with clinical populations of the disorder (Kulacaoglu & Kose, 2019; Paris, 2020). Further, BPD is characterized by coping behaviors that borderlines use to essentially control, react to, or manipulate their environment to feel safe or to diffuse anxiety (Paris, 2020; Sperry, 2016). These include idealization, devaluation, projection, projective identification, splitting, gaslighting, intermittent reinforcement, omnipotence; and conversion, somatization, denial, detachment, derealization, and depersonalization (related to dissociation; Mancinelli et al., 2024; Mazinan et al., 2024; Nemeh & Khandai, 2024; Sperry, 2016; Paris, 2020).

Classification of BPD is informed by variety of combinations of symptoms, including their absolute and comparative magnitudes (severity), duration, and frequency (oscillatory behavioral dynamics), and transdiagnostic neuropsychological markers. The above symptomatic and coping features combined with comorbidities discussed previously contribute to the behavioral, phenomenological, and nosological heterogeneity of BPD resulting in a plurality of types (classes) and subtypes (subclasses) of BPD (high dimensional classification), arguably supporting the search for differentiating endophenotypes and deep endophenotypes of the disorder (Lenzenweger et al., 2008).

Numerous person-centered (informed by object relations theoretical concepts) qualitative and quasi-quantitative approaches have been used to segregate BPD subclasses. These methods have resulted in numerous subtypes of BPD, such as, autonomous, dependent, vindictive, moderate submissive, nonassertive, exploitable, socially avoidant, internalizing dysregulated, externalizing dysregulated, histrionic-impulsive, high functioning internalizing, histrionic, depressive internalizing, angry externalizing, withdrawn internalizing, severely disturbed internalizing, anxious internalizing, discouraged, impulsive, petulant, self-destructive, and even classifications of waif (an internalizing form driven by helplessness and victimization), hermit (an avoidant form driven by fear and persecution), queen (a histrionic grandiose pathological narcissist form), witch (similar to the BPD-malignant narcissist subtype described previously that can have annihilating borderline rage), and medean witch (similar to the BPD-malignant narcissist with antisocial, psychopathic, and dark triad features subtype described previously) in respect of borderline mothers (Lawson, 2004; Smits et al., 2017). In line with psychoanalytic categorization, a possible model of high level classification can also arguably divide BPD into ego syntonic and ego dystonic high level subtypes that can correlate with, on the one hand (ego syntonic), externalizing BPD populations with poor prognosis, who don't seek treatment due to lack of insight into their illness, and most often are comorbid with other cluster B personality disorders, and, on the other hand (ego dystonic), internalizing BPD populations with better prognosis, who seek treatment due to insight into their illness, are often suicidal, and, to the extent comorbid with a personality disorder, are most often are comorbid with cluster A and cluster C personality disorders; with both subtypes commonly comorbid with Axis I psychiatric disorders.

Numerous variable centered quantitative approaches have been used to segregate BPD subclasses. They have included various forms of dimensional reduction (e.g., exploratory factor analysis [EFA] or confirmatory factor analysis [CFA]), latent class analysis, finite mixture modeling, and clustering methods (Brown, 2024; Lenzenweger et al., 2008; Smits et al., 2017; see also section on neurocomputational methods). These methods have resulted in factors such as psychosis subtype, core subtype, affectless, defended, as-if subtype, neurosis subtype, nonaggressive/nonparanoid/nonantisocial subtype, paranoid/nonaggressive/nonantisocial subtype, aggressive/antisocial/nonparanoid subtype, and, logically, aggressive/antisocial, paranoid subtype; emotional/disinhibited, low anxiety/antisocial, inhibited/internalizing /avoidant, angry-aggressive, angry-mistrustful, poor identity-low anger, prototypical, extravert-externalizing, schizotypal, core BPD, narcissistic-histrionic-antisocial, low psychopathology, high psychopathology, internalizing, and externalizing (often characterized by high impulsivity and impulsive anger), among many others (Brown, 2024; Lenzenweger et al., 2008; Oladottir et al., 2022; Smits et al., 2017). Such methods to classify often employ the tools of artificial intelligence (AI). The use of AI methods, including machine learning (ML) and deep learning (DL), for classification of borderline personality disorder is discussed later in this chapter in the section discussing neurocomputational methods.

Use of Neuropsychological Measures to Inform BPD Diagnosis. Because BPD is so difficult to diagnose and treat in most patients, proper diagnosis benefits from comprehensive neuropsychological and psychometric testing, including use of sophisticated self-report measures, such as the Minnesota Multiphasic Personality Inventory (MMPI-2), Millon Clinical Multiaxial Inventory (MCMI-IV), and projective tests, such as the Rorschach and Thematic Appreciation Test (TAT; Ajnkya et al., 2021; Bozatello et al., 2021; Sperry, 2016). Due to

delusional mental states, identity diffusion, and projective identification and, in ego syntonic patients, a profound lack of insight into their illness, borderlines are generally not reliable self-reporters in many respects so self-report measures can be of limited utility in BPD patients (Gunderson et al., 2018; Paris, 2020; Sperry, 2016). Consequently, tests with strong validity scales are important due to BPD patients often delusional mental states or projection, or intentional deception or dishonesty and mischaracterization of facts that make even structured interviews or use of more simple self-report measures produce questionable or inaccurate results (Gunderson et al., 2018; Paris, 2020; Sperry, 2016).

More specific and rigorous psychometric tests designed specifically for BPD, such as the personality assessment inventory – borderline features scale (PAI-BOR) and the diagnostic interview for borderlines (DIB-R) can help refine and confirm BPD diagnosis (Bassir Nia et al., 2018; Gunderson et al., 2018; Paris, 2020; Tragesser et al., 2010). The DIB-R, for example, measures all three of the above domains (thinking, feeling, acting; Gunderson et al., 2018; Paris, 2020; Tragesser et al., 2010). Further, it may be useful to inform diagnoses of certain particularly challenging and extreme subclasses of BPD psychopathology, such as those co-morbid with NPD and APD (malignant narcissism discussed above) that can thus include use of additional instruments, including the psychopathic personality inventory-revised (PPI-R; particularly use of the self-centered impulsivity [SCI] scale), pathological narcissism inventory (PNI), brief symptom inventory (BSI), multidimensional personality questionnaire (MPQ), state-trait anger expression inventory-2 (STAXI-2), international personality disorder examination (IPDE) and generation of a malignant narcissism (MALNAR) index (Cain et al., 2024; Lenzenweger et al., 2018). For a more comprehensive list of neuropsychological measures, see Bozzatello et al. (2021) and Gunderson et al. (2018). For a comprehensive list of neuropsychological measures

used as outcome measures to evaluate the efficacy of psychotherapeutic interventions, see Wibbelink et al. (2022).

In the context of improved differential diagnosis, use of a suite of measures, including laboratory behavioral measures (e.g., the go/no-go task) to characterize various symptoms, such as impulsivity, including facets of behavioral response inhibition, can inform diagnosis, including the diagnosis of extreme forms of BPD, such as comorbid with malignant narcissism, within BPD, by decomposing the various facets and dimensions of impulsivity to create deep endophenotypes (Cain et al., 2024; Gunderson et al., 2018; Lenzenweger et al., 2018; Sperry, 2016; Paris, 2020). For example, BPD patients have shown marked elevated scores on all subscales of impulsivity measured by the BIS-11 (Paris, 2020). For a comprehensive list of studies of differential diagnosis of BPD, see Bozzatello et al. (2021).

Prototypical BPD Behavioral Phenotype. BPD may be the most severe of all personality disorders, most difficult to diagnose and understand, most difficult to treat, and presents the most complex and plural presentation of impulsivity and disinhibition (deficits in BRI; Bozzatello et al., 2021; Kernberg, 2004; Paris, 2020; Sperry, 2016). Consequently, it is helpful to understand a typical behavioral dynamic presentation, including contextually understanding the extreme role impulsivity has in the disorder. Due to their cognitive distortions (including transient delusions and identity diffusion), BPD patients over mentalize others in a misguided attempt to leverage their highly empathic abilities to read (or misread) the intentions of others, and project hypersensitive fears of rejection and abandonment onto others (Gunderson, 2011; Gunderson et al., 2018; Paris, 2020; Schurz et al., 2024; Sperry, 2016). This includes projective identification, where the other inadvertently assumes the projection, in effect validating it (Paris, 2020; Sperry, 2016). This leads to enduring emotional dysregulation

(including severe anxiety, even panic) in the borderline comprising hyperbolic emotional arousal states perceived by them as externally triggered by stressors, which are validated by their internal cognitive distortions and projective identification (Gunderson, 2011; Paris, 2020; Sperry, 2016). In this respect, invoking Linehan (1993), projection (and, more specifically, projective identification) may be viewed as a form of self-validation by borderlines who lacked validation by caregivers during childhood.

BPD patients then operationalize their emotional dysregulation in an effort to quiesce, blunt, transfer, or dissociate from their anxiety through irritable mood states that manifest as internalizing self-harm (including suicidal behavior) or externalizing impulsive aggression and so called *borderline rage* (Greenberg, 2016; Gunderson, 2011; Guzmán et al., 2024; Leucci et al., 2024; Paris, 2020; Sperry, 2016; Wojciechowski, 2021). Borderline rage is often targeted at those they fear to lose (often leading to intimate partner domestic violence [IPV], including both physical and emotional abuse, particularly, or more extremely, when BPD is comorbid with malignant narcissism) in an idealization/devaluation push-pull self-fulfilling cycle of abandonment that is a form of coping-dissociation through splitting of others (Greenberg, 2016; Gunderson, 2011; Guzmán et al., 2024; Leucci et al., 2024; Paris, 2020; Sperry, 2016). To further manage their sense of emotional overwhelm, BPD patients also often engage in impulsive self-medication through cutting, substance abuse, alcohol abuse, or risky or prolific sexual activity, or via dissociation, depersonalization, derealization, and detachment (Gunderson, 2011; Mazinan et al., 2024; Paris, 2020). Consequently, severe impulsive behavior is the harmful byproduct of cognitive distortions and emotional dysregulation (Gunderson, 2011; Paris, 2020; Sperry, 2016; Wojciechowski, 2021).

However, as suggested by the discussion of NDST theory earlier in this chapter, feedback loops dictate interactions between self and other and self and false self, including between one's projections. Negative environmental feedback to a BPD patient's impulsive behavior, then exacerbates or leads to more cognitive distortions, since the patient lacks a sense of self and further lacks insight into their endogenous contribution to their exogenous triggers and stressors, resulting in an escalating negative feedback loop that is the borderline cycle (Gunderson, 2011; Paris, 2020). Co-oscillating with the negative feedback loop is a positive feedback loop that is the product of their idealization phase or their cry-for-help phase where they manipulate others to meet their attachment needs (Paris, 2020; Sperry, 2016). Stressors and triggers, even slight ones (a product of constitutional interpersonal hypersensitivity), can easily cause a phase shift from positive valence to negative valence in a borderline and in associated feedback loops (Paris, 2020; Sperry, 2016). Impulsivity begets impulsivity.

Current Treatment Paradigms for BPD. BPD is perhaps the most dreaded mental disorder for clinicians to treat, with most clinicians assuming it is untreatable and further assuming that such patients are unpleasant to treat and may pose a threat (Gunderson et al., 2018; Kernberg & Michels, 2009; Nemeh & Khandai, 2024; Paris, 2020; Sperry, 2016; Trimboli & Marshall, 2020; Vogt & Norman, 2022). Even insurance companies may often charge higher malpractice premiums if a clinician has any material measure of BPD patients in their treatment pool, due, at least in part, to adverse outcomes, including harm to self and others (Krasner, 2017). However, particularly with respect to low functioning ego dystonic BPD patients who seek treatment, there are numerous treatment modalities that have shown sufficient efficacy to place such patients into enough remission to become functional (Crotty et al., 2024; Gunderson et al., 2018; Kernberg & Michels, 2009; Mendez-Miller et al., 2022; Paris, 2020; Sperry, 2016;

Trimboli & Marshall, 2020). Rather than psychopharmacological intervention, as is the case with ADHD and schizophrenia, like with ASD, the standard of care for BPD is one or more of a suite of specialized and targeted psychotherapeutic interventions (Crotty et al., 2024; Mendez-Miller et al., 2022; Mungo et al., 2020; Nemeh & Khandai, 2024; Paris, 2020, Sperry, 2016). However, the National Institute for Health and Clinical Excellence (NICE) recommends psychotherapy coupled with short term psychopharmacological treatment for BPD (Mungo et al., 2020).

Dialectical Behavior Therapy. There appears to be some consensus in the literature that the most effective, most researched, and most validated treatment modality in BPD clinical populations is dialectical behavioral therapy (DBT), developed by Marsha Linehan (Choi-Kain et al., 2017; Gunderson, 2011; Gunderson et al., 2018; Linehan, 1993; Lombardo et al., 2023; Lynch et al., 2007; Mendez-Miller et al., 2022; Nemeh & Khandai, 2024; Sperry, 2016; Wibbelink et al., 2022). However, some studies have had mixed results or failed to materially distinguish DBT from other modalities (Crotty et al., 2024). Nonetheless, as much as 50% of DBT patients go into remission (Wibbelink et al., 2022). DBT approaches BPD as primarily an emotional dysregulation disorder (Choi-Kain et al., 2017; Gunderson, 2011; Lynch et al., 2007; Wibbelink et al., 2022). It combines cognitive behavioral therapy with mindfulness (Zen Buddhist influence) therapy through a structured, integrative, and intensive team-based treatment program (Linehan, 1993; Lynch et al., 2007; Sperry, 2016; Wibbelink et al., 2022). Because DBT assumes a childhood invalidating environment is central to BPD, DBT therapy first begins by validating the internal reality and experience, albeit a false reality of the patient, termed radical acceptance (Lynch et al., 2007; Wibbelink et al., 2022). It then confronts the dialectic of extremes, radical acceptance coupled with transformation of their inner experience (Sperry,

2016; Wibbelink et al., 2022). DBT's efficacy at treating impulsivity in BPD patient samples has not been definitively demonstrated (Mungo et al., 2020).

Mentalization Based Psychotherapy. Mentalization based therapy (MBT) is a psychodynamic/psychoanalytic treatment modality that has also shown to be efficacious in BPD clinical samples, particularly with respect to anxiety and depressive symptoms (Choi-Kain et al., 2017; Crotty et al., 2024; Bateman & Fonagy; Gunderson, 2011; Mendez-Miller et al., 2022; Nemeh & Khandai, 2024; Sperry, 2016; Vogt & Norman, 2022). It treats BPD as primarily a self-disorder and focuses on both cognitive distortions (particularly the fragmented sense of self) and emotional dysregulation, applying attachment theory, theory-of-mind, and object relations theory (Gunderson, 2011; Vogt & Norman, 2022). Mentalization based psychotherapy focuses more on cognitive distortions than emotional dysregulation, keeps a clean separation between patient and therapist, avoids activation of emotions, and concentrates on helping the patient interpret their inner distorted experience through curiosity (not knowing) rather than challenging it (Choi-Kain et al., 2017; Bateman & Fonagy, 2016; Vogt & Norman, 2022). As suggested above, impulsivity in BPD patients is generally reactionary to their internal cognitive distortions through emotional dysregulation, projections of those distortions onto others, and triggers from real or imagined stressors (Sperry, 2016). Consequently, addressing the former may reduce the latter by not triggering it (Bateman & Fonagy, 2016; Sperry, 2016). Indeed, mentalization based psychotherapy has been shown to be efficacious at treating impulsivity in BPD patient samples (Mungo et al., 2020).

Transference Based/Focused Psychotherapy. Transference based/focused psychotherapy (TBP/TFP) is also a psychodynamic/psychoanalytic treatment modality efficacious in BPD clinical samples (Choi-Kain et al., 2017; Clarkin et al., 2015; Crotty et al., 2024; Gunderson, 2011; Kernberg, 1984; Kernberg, 2018; Seyed Asl et al., 2024; Sperry, 2016). It similarly approaches BPD as primarily a self-disorder, in light of theory-of-mind and object relations theory, targeting cognitive distortions and emotional dysregulation more equally than mentalization based psychotherapy does (Clarkin et al., 2015; Gunderson, 2011; Kernberg, 1984; Kernberg, 2018; Seyed Asl et al., 2024; Sperry, 2016). Transference based psychotherapy supports more integration in the patient-therapist dyad (transference and countertransference) where the therapist is integral to activate emotions in the patients by challenging or confronting their cognitive distortions of self and other (Clarkin et al., 2015; Gunderson, 2011; Seyed Asl et al., 2024; Sperry, 2016). That process helps the patient integrate incompatible emotional experiences of all good and all bad splitting of self and significant others (an object relations dysfunction), for example (Clarkin et al., 2015; Seyed Asl et al., 2024; Sperry, 2016). This lack of integration is the spark that lights the fire of impulsive aggression and other manifestations of impulsivity in BPD patients (Sperry, 2016).

Schema Focused Psychotherapy. Schema focused therapy has also been shown to be efficacious in BPD patient samples (Choi-Kain et al., 2017; Crotty et al., 2024; Wibbelink et al., 2022). It was developed by Jeffry Young, a student of the developer of cognitive behavioral therapy, Aaron Beck (Gunderson, 2011; Sperry, 2016; Young et al., 2006; Wibbelink et al., 2022). Schema-based therapy draws from numerous theories including attachment theory, object relations theory, gestalt methods, and psychodynamic approaches (Sperry, 2016; Young et al., 2006). It parses personality into schemas and focuses on maladaptive schemas: insufficient self-

control, abandonment; defectiveness, mistrust/abuse, emotional, and isolation (Sperry, 2016). It also proposes BPD specific schema modes of angry/impulsive child, abandoned/abused child, punitive parent, and detached protector (Choi-Kain et al., 2017; Mungo et al., 2020). Schema therapy has been shown to be particularly effective at treating impulsivity in BPD patient populations (Mungo et al., 2020).

Other BPD Psychotherapeutic Modalities. General (good) psychiatric management has also shown some efficacy for the treatment of BPD (Choi-Kain et al., 2017; Crotty et al., 2024; Gunderson, 2011; Gunderson, 2014; Gunderson et al., 2018; Nemeh & Khandai, 2024). System training of emotional prediction and problem solving (STEPPS) is a short term (20 weeks) treatment that has shown efficacy in BPD patient samples (Choi-Kain et al., 2017; Crotty et al., 2024; Mungo et al., 2020). STEPPS has shown significant efficacy in reducing impulsivity, particularly in BPD patient samples with comorbid antisocial personality disorder (Mungo et al., 2020). Cognitive behavioral therapy (CBT; and general supportive therapy), the most popular of all psychotherapeutic treatment modalities for DSM disorders, has shown to be less effective or not at all effective with many borderline patients although the heterogenous nature of BPD behavioral phenotypes suggests they may be efficacious in certain clinical samples (Crotty et al., 2024; Sperry, 2016). Other psychotherapeutic interventions include dynamic deconstructive psychotherapy (DDP), acceptance and commitment therapy (ACT), and manual assisted cognitive therapy (MACT; Crotty et al., 2024).

Psychopharmacological Interventions. There are no psychopharmacological interventions that specially target BPD or that have been shown to successfully treat BPD broadly (Choi-Kain et al., 2017; Gartlehner et al., 2021; Herpertz et al., 2007; Nemeh & Khandai, 2024; Pascual et al., 2023). However, polypharmacy is a common treatment approach

for BPD with over 80% and as much as 96% of BPD patients on psychotropic intervention, 40-50% of BPD patients prescribed three or more psychotropic interventions, almost 20% four or more, and 10% prescribed five or more (Gartlehner et al., 2021; Gunderson et al., 2018; Herpertz et al., 2007; Mendez-Miller et al., 2022; Pascual et al., 2023; Riffer et al., 2019). Most psychotropic interventions target symptoms or comorbid disorders of BPD rather than BPD itself (Gartlehner et al., 2021; Gunderson, 2011; Gunderson et al., 2018; Herpertz et al., 2007; Paris, 2020; Pascual et al., 2023).

SSRI's are the most common psychopharmacological intervention for BPD and typically prescribed to address borderline depression and impulsivity, but have shown limited efficacy in this clinical population (Choi-Kain et al., 2017; Gartlehner et al., 2021; Gunderson, 2011; Gunderson et al., 2018; Herpertz et al., 2007; Mendez-Miller et al., 2022; Paris, 2020; Pascual et al., 2023; Riffer et al., 2019). Benzodiazepines are often prescribed to alleviate anxiety symptoms (Gartlehner et al., 2021; Pascual et al., 2023). Atypical antipsychotics have shown efficacy in BPD patients, particularly olanzapine to address delusional states and transient psychotic episodes (Choi-Kain et al., 2017; Gartlehner et al., 2021; Gunderson, 2011; Herpertz et al., 2007; Paris, 2020; Pascual et al., 2023; Riffer et al., 2019; Sperry, 2016). Quetiapine (Seroquil) is a popular antipsychotic in BPD patients because it also treats impulsive aggression and anxiety, common targets for intervention by antipsychotics (Gartlehner et al., 2021; Mendez-Miller et al., 2022; Riffer et al., 2019; Pascual et al., 2023; Sperry, 2016). Aripiprazole has been shown to be particularly effective in treating impulsivity in BPD clinical samples (Mungo et al., 2020). Mood stabilizers, such as lamotrigine, have also shown to be efficacious (Choi-Kain et al., 2017; Gartlehner et al., 2021; Gunderson, 2011; Herpertz et al., 2007; Pascual et al., 2023; Riffer et al., 2019). Anticonvulsants are also more and more commonly used for the treatment of

BPD to address impulsive anger in addition to impulsiveness generally and broader affective dysregulation (Gartlehner et al., 2021).

However, again, DBT and other targeted psychotherapeutic modalities are the standard of care for BPD, not psychopharmacology, with many believing psychopharmacology is not necessary or can be harmful to BPD patients (Crotty et al., 2024; Gartlehner et al., 2021; Paris, 2020; Riffer et al., 2019). For example, benzodiazepines, such as diazepam (Valium), alprazolam (Xanax), lorazepam (Ativan), clonazepam (Klonopin), and temazepam (Restoril) are prescribed to as much as 60% of BPD patients to relieve anxiety that is so prevalent (as much as 80%) among the BPD clinical population (Pascual et al., 2023). However, benzodiazepines have been shown to undermine BRI leading to behavioral disinhibition and thus impulsivity, which can then exacerbate a borderline patient's propensity for substance use disorders, also common in BPD patients, where benzodiazepines often lead to addiction in the general population (Pascual et al., 2023). This is a reasonable observation in light of the previous discussion between the somewhat orthogonal relationship between impulsivity (stimulation seeking) and compulsivity (anxiety reducing) behavior. Even psychopharmacological treatment of one or more symptoms of BPD, including impulsivity, is not typically recommended as a first line treatment (Gartlehner et al., 2021; Pascual et al., 2023). Indeed, it is the multifactorial features of BPD and its comorbidities that can confound and complicate polypharmacy, which many psychiatrists may be unable to reconcile as they often focus on symptom relief rather than differential diagnosis of all comorbidities and thoughtful administration of polypharmacy informed by proper diagnosis and contraindications considerations. While psychotherapy is the first line treatment, polypharmacy is not only common, but often recommended.

Integrative Multimodal Psychotherapy. The above is not to suggest that DBT is the best modality for all patients or other modalities less effective for any given patient than DBT. Behavioral phenotypes for BPD come in many combinations (Vogt & Norman, 2022). As discussed above, there are countless subtypes of BPD, each that can respond or not respond to different types of treatment. In fact, calculating the sums of binomial coefficients of combinations of five or more of nine categories of the DSM criteria provides at least 256 dimensionally distinct borderline behavioral phenotypes and that number does not include further stratification of BPD into magnitude and weight of dimensional dysfunction or into categories of comorbidities and combinations of comorbidities described previously, which greatly increases subclassification of this behavioral phenotype, including whether a patient is ego syntonic (has no insight) or ego dystonic (has insight) into their disorder. DBT (and other modalities, such as schema therapy) is likely a better choice for those who are ego dystonic, have insight into their illness, include suicidal ideation and behaviors in their symptom presentation, have trauma histories, seek treatment, and are low functioning (Sperry, 2016; Wibbelink et al., 2022). DBT may be less effective or not effective at all with a high functioning ego-syntonic borderline with no insight into their illness who would need to be compelled into treatment or who is more likely to drop out of treatment (Paris, 2020; Sperry, 2016; Trimboli & Marshall, 2020; Wibbelink et al., 2022).

Similarly, due to its heterogeneity, psychopharmacological interventions may be efficacious in certain BPD clinical populations and have shown to be useful for at least 30% of the BPD clinical population (Kernberg & Michels, 2009). Notwithstanding the forgoing, a near majority of BPD patients do not respond to psychopharmacological interventions or specialized psychotherapy at all (Wibbelink et al., 2022). For many BPD patients, particularly severe

presentations of the disorder, an integrative multimodal therapeutic approach may be most effective, combining polypharmacy with a plurality of the above specialized psychotherapeutic interventions (Herpertz et al., 2007; Sperry, 2016). This would include neurophysiological interventions, such as transcranial magnetic stimulation (TMS) that are now being studied as BPD treatment modalities (Mungo et al., 2020). Again, treatments focused on impulsivity and deficits in BRI may present the best opportunity for treatment efficacy and decomposed facets of BRI and impulsivity may be the most promising putative endophenotypes of BPD. Table 7 compares the above four behavioral phenotypes across certain characteristics.

Table 7

Heritability, Prevalence, and Clinical Characteristics of Target Behavioral Phenotypes

Disorder	Herit. (%)	Prev. (%)	Age of Onset	Gender (M:F)	Core BRI Deficit	Impulsivity Severity	Treatment Response
ADHD	74-88	7-15	< 7	2-4:1	Primary	High	Good (stimulants)
ASD	73-93	1-2.2	2-7	4-5:1	Secondary to compulsivity	Mod-High	Variable (behavioral)
Schizopr	50-80	1	17-25	1:1	Severe	Very High	Poor (antipsychotics)
BPD	40-70	2-6	20+	1:3 (clin)	Most Severe	Extreme	Poor (psychotherapy)

Note: Hert. = heritability, Prev. = prevalence. Schizopr. = schizophrenia.

Endophenotypes of Behavioral Response Inhibition (BRI)

Consistent with the premise of the RDoC, endophenotypes of behavioral response inhibition (BRI) fall along a transdiagnostic and scale agnostic continuum of units of analysis, which comprise measures. Each measure can serve as an endophenotype of BRI, and even when taken as a group, can comprise a deep endophenotype. Certain measures are proxies for latent constructs or sub-constructs that cannot be measured directly. BRI is one such construct. In the RDoC matrix, psychological constructs such as impulsivity or BRI, for example, will appear under RDoC domains and their measures will appear under units of analysis (NIMH, 2023). An endophenotype can be the construct or subconstruct (a latent endophenotype in this case), or any one of its measures across scales of units of measure and analysis (i.e., the deep endophenotype). The RDoC lists eight categories of units of analysis from genotype through categories of endophenotypes as proxies for constructs and subconstructs through units of analysis and their measures.

Along an upscaling continuum, the units of analysis in the RDoC are genotype, molecules, cells, circuits, physiology, behaviors, self-reports, and paradigms (NIMH, 2023) and can be used to assemble or map a deep endophenotype of BRI or other construct. Each unit of analysis has many units of measure (potentially enabling local deep endophenotypes). For example, in the context of the units of analysis (measures) relevant to this study, the Molecule unit of analysis includes dopamine (NIMH, 2023). The Cells unit of analysis includes dopaminergic neurons (NIMH, 2023). The Circuits unit of analysis includes both neuroanatomical loci, such as the ACC and dlPFC, and neural circuits, such as the corticolimbic circuit (NIMH, 2023). The Physiology unit of analysis includes EEG/ERP components (NIMH, 2023). The Behaviors unit of analysis includes impulsivity and BRI (through their measures;

NIMH, 2023). The Self-Reports unit of analysis includes the BIS-11 (NIMH, 2023). The Paradigms unit of analysis includes the go/no-go task (GNG) and stop signal task (SST; NIMH, 2023).

Note that, as of 2017, the NIMH removed individual genes from the Genes unit of analysis due, at least in part, to the issue of small effect size of candidate genes, since such unit of analysis would list such candidate genes and, notwithstanding that GWAS studies are welcomed by the RDoC, that is still the case as of 2024 (NIMH, 2024). If studies, such as this study, can better discriminate endophenotypes associated with their genotypes, the effect size of given candidate genes may be improved to be acceptable for use in RDoC studies, although an RDoC study such as this study can also be used with traditional candidate genes studies. At any rate, the first five categories of RDoC units of analysis comprise potential neurobiological and neurophysiological endophenotypes and the final three categories comprise potential neuropsychological endophenotypes. These are discussed next in the context of impulsivity and BRI.

Neurobiological Endophenotypes

Neurobiological correlates of the psychological constructs of impulsivity and behavioral response inhibition (BRI) include brain regions (neuroanatomical loci) and brain circuits (neural network systems). Following the previously described premise that behavior is the phenotypic output of the brain, brain regions and circuits are activated by impulsive thoughts (cognitions) and actions (behavior) or by engagement, or lack thereof, of executive functions (EF's) or inhibitory systems necessary to perform goal directed tasks (Perez-Edgar & Fox, 2018). For example, the research literature has implicated, among others, the following brain regions in BRI: inferior prefrontal cortex (iPFC), right inferior frontal cortex (rIFC), right inferior frontal

gyrus (rIFG), subthalamic nucleus (STN), pre-supplementary motor area (preSMA), supplementary motor area (SMA), orbitofrontal cortex (OC), dorsolateral prefrontal cortex (dlPFC), insula, and anterior cingulate cortex/gyrus (ACC; Aron et al., 2007; Aron et al., 2014; Bhaijiwala, 2016; Dattola et al., 2020; Gholamipourbarogh et al., 2023; Hampshire & Sharp, 2015; Isherwood et al., 2023; Jonas & Markon, 2014; Luijten et al., 2014; Moeller et al., 2005; Powers et al., 2022; Stalnaker et al., 2015; Waldthaler et al., 2022; Wilburtz et al., 2014). Brain regions implicated for BIS-11 measured trait impulsivity include the dlPFC, ACC, and OC (Besteher et al., 2019).

The literature has also implicated several brain circuits (neural networks) in BRI. For example, as discussed previously, different neural network systems (brain circuits) and neuroanatomical loci (brain regions) are implicated when executive functions necessary for BRI are engaged than when they are bypassed. With respect to brain circuits, the process of premeditation and precognition enlists dopaminergic mesocortical brain circuits that project from the medial ventro tegmental area (VTA) of the limbic system to the prefrontal cortex (Kabanova, et al., 2015; Reneaux et al., 2015). When executive functions are not engaged in deficient BRI, the PFC is not engaged, and mesolimbic circuits that project from the VTA to the ventral striatum, primarily the nucleus accumbens (NAcc) are primarily active (Kabanova, et al., 2015; Reneaux et al., 2015). As mentioned above, neuroanatomical loci implicated in BRI include the dorsolateral prefrontal cortex (dlPFC), right inferior frontal gyrus (rIFG), and anterior cingulate cortex (ACC). Communication between these regions for BRI occurs via fronto-striatal neural networks from the prefrontal cortex to the basal ganglia (Waldthaler et al., 2022). While implicated brain regions and circuits can serve as candidate endophenotypes of psychological constructs, as discussed previously, the psychological constructs are typically latent variables

that are operationalized through variables comprising their measurement, and those measures can also be candidate endophenotypes in their own right.

Neuroimaging and Neurophysiological Measures as Endophenotypes. Applying the RDoC matrix's units of measure, neurobiological correlates of BRI have been operationalized via neuroimaging and neurophysiological instruments including fMRI and qEEG/ERP. Consequently, it is the output measures of these instruments that can comprise neurobiological endophenotypes. Based on the literature search for this study, fMRI and qEEG/ERP are the most common and pervasively published neuroimaging modalities in the impulsivity and BRI RDoC endophenotype literature as well as DSM focused research literature, although fNIRS studies have been appearing with greater and greater frequency in recent years. Consequently, each of these methods is discussed first in detail and are the primary neuroimaging methods for neurobiological endophenotype studies discussed in this chapter. However, there are a number of additional neuroimaging methods (including fNIRS), both functional and structural, that have been used in related research on impulsivity and BRI and related behavioral phenotypes as endophenotypes or as measures comprising endophenotypes. While there are fewer studies using these methods than fMRI or qEEG/ERP, arguably because they are both costly and more invasive in some cases, they continue to show promise and potential to inform the BRI endophenotype and related behavioral phenotype research literature for both RDoC studies and classical DSM focused studies. These methods include DTI, MEG, PET, SPECT, and fNIRS and are more briefly discussed after fMRI and qEEG/ERP and all summarized in Table 8. As suggested above, fNIRS, in particular, has promise for further use in the endophenotype literature.

fMRI. Functional magnetic resonance imaging (fMRI) looks at neuroanatomical functional locations (brain regions) using hemodynamics through blood oxygenation level dependent (BOLD) imaging as a proxy for activation (firing) of neurons (brain activity; Aron et al., 2014; Bhaijiwala, 2016; Bohon et al., 2020; Chevrier et al., 2007; Janssen et al., 2018; Pan et al., 2021). Although fMRI has high spatial resolution, in the millimeter range, enabling identification of precise functional locations (loci) for latent activation of neurons, it has poor temporal resolution, of seconds at best, so it is not useful to precisely measure activity of entire brain circuits (neural networks; Aron et al., 2014; Congdon, 2008; Hampshire & Sharp, 2015; Luck, 2014).

In fMRI studies, which have high spatial resolution, the relationship between genotype and endophenotype is often linked via reductionist functional neuroanatomical locations, such as the dorsolateral prefrontal cortex (dlPFC) and anterior cingulate cortex (ACC), both representative of high concentrations of DRD4 epigenetic gene expression, or the right inferior frontal cortex (rIFC), which has been suggested to be a neuroanatomical module of inhibitory control (Aron et al., 2014; Bidwell, 2009; Congdon, 2008; Hampshire & Sharp, 2015; Robbins, et al., 2003). However, that relationship is far less often linked via distributed dynamical systems represented by the dynamic behavior of neural network circuit systems, such as the dopaminergic mesolimbic, mesocortical, and nigrostriatal neural networks, differentiated by facet or subtype of BRI or impulsivity, but agnostic to functional neuroanatomical location (Aron et al., 2014; Bidwell, 2009; Congdon, 2008; Hampshire & Sharp, 2015; Robbins et al., 2003).

qEEG/ERP. Quantitative electroencephalography is a quantitative neuroimaging method that uses event related potentials (qEEG/ERP) to measure brain activity by detecting electrical impulses emitted by pyramidal neurons that fire just beneath the scalp (Dattola et al., 2020;

Luck, 2014). Neuronal firing oscillates across distance and a time series as multiple neurons synchronize along a brain circuit and these oscillations occur at different frequencies referred to as brain waves (Luck, 2014). If a series of EEG measurements are taken during an evoked event (a perturbation), such as a button push from a task related to a neuropsychological measure (see next section), and (after removal of noise and other known artifacts) averaged, the result identifies measurable positive and negative peaks (ERP components) during stable time locked intervals (epochs) that follow the event, such that each epoch has a unique wave form signature (Luck, 2014). While qEEG/ERP has sufficient temporal resolution (milliseconds) to enable measurement of neural dynamics, it has poor spatial resolution (centimeters at best, Luck, 2014). This illustrates a contrast with fMRI that is a focus of much debate in the literature, with some camps focused on functional locations and others on neural networks and their dynamics.

Nomenclature of ERP components typically codes positive (P) or negative (N) peaks with either the time (in milliseconds) or order of the peak's appearance (e.g., N200 or N2). Counterintuitively, due to electrical dynamics of spike trains, positive peaks are oriented downward and negative peaks oriented upward. Several ERP components, such as P300 (P3), are often considered candidate endophenotypes of behavioral phenotypes, such as schizophrenia, as well as of executive functions, impulsivity, motor inhibition, and BRI (Dattola et al., 2020; Huster et al., 2020; Menkes et al., 2022; Sperl et al., 2021, Trutsky et al., 2015; Waller et al., 2021). Often, waveform signatures comprising complexes of ERP's (e.g., N2/P3) also serve as candidate endophenotypes (Menkes et al., 2022; Skippen et al., 2020; Wessel, 2017). These are discussed in more detail later in this chapter.

As mentioned above, neuroimaging and neurophysiological methods with high temporal resolution, such as qEEG/ERP, which is based on electromagnetism, can be used to identify

neurophysiological endophenotypes for impulsivity and BRI, including ERP components or ERP waveform complexes as endophenotypes of neuropsychiatric disorders (behavioral phenotypes), such as schizophrenia, ADHD, and bipolar disorder, to inform differential diagnoses (Chun et al., 2013; Luck et al., 2011). Shahaf and Pratt (2013), for example, used qEEG/ERP to characterize impulsivity and BRI using the go/no-go (GNG) behavioral task in ADHD subjects. Braunstein (2014) used qEEG/LORETA (discussed below) and a behavioral test of sustained attention, the Conner's continuous performance test (CCPT), to study the anterior cingulate cortex (ACC) and the executive function deficiency of inattention, which is a behavioral phenotype of ADHD. Tye et al. (2011) studied ADHD endophenotypes using qEEG/ERP. The above studies, and most others that utilize qEEG/ERP to study endophenotypes, however, focused on clinical disorders and patient populations, rather than RDoC informed non-clinical populations.

Further, as noted above, while qEEG/ERP has high temporal resolution, on the order of milliseconds (vs. seconds for fMRI), it has poor spatial resolution, on the order of centimeters at best and undefined at worst (vs. millimeters for fMRI; Luck, 2014). To address the poor spatial resolution of qEEG/ERP while benefiting from its high temporal resolution, low resolution brain electromagnetic tomography (LORETA), such as that used by Braunstein (2014) above, was developed in 1994 (Dattola et al., 2020). LORETA is an algorithmic set of computational tools that utilize an inverse solution to the Poisson equation (the inverse problem) to estimate cortical electrical current density from EEG electrode linear colocations to generate statistical three-dimensional cerebral maps of brain activity to provide spatiotemporal functional location information including using standardized locations of EEG electrodes (see below; Cannon, 2012; Grech et al., 2008; Dattola et al., 2020; Pascual-Marqui, 2002; Pascual-Marqui, 1999). LORETA generates images co-registered on a standard MRI (Talairach) atlas image with spatial resolution

on the order of five millimeters (Cannon, 2012; Dattola et al., 2020; Jatoi et al., 2014; Pascual-Marqui, 2002; Pascual-Marqui, 1999). Consequently, LORETA provides functional localization of time locked ERP events that can aid in the localization of dynamic neural network activity for behavioral endophenotypes, such as behavioral response inhibition (BRI; Cannon, 2012; Pascual-Marqui, 2002; Pascual-Marqui, 1999). Evolutions of LORETA to improve its spatial resolution include standardized LORETA (sLORETA), which improves localization error by standardizing the current density, and exact LORETA (eLORETA), which reduced localization error even more (Dattola et al., 2020). eLORETA is arguably the current state of the art for spatiotemporally optimized qEEG/ERP computational neuroimaging. eLORETA “provides a genuine inverse solution which provides exact localization with zero error in the presence of measurement and structured biological noise” (Jatoi et al., 2014, p. 715). As the state-of-the-art progresses, newer methods utilizing explainable artificial intelligence (XAI), for example, have applied machine learning and convolutional neural networks (CNN) from deep learning (see neurocomputational methods section below), such as SHERPA to identify ERP components (Sylvester et al., 2023).

It is important to note that, compared to virtually all other neuroimaging methods described here (but see fNIRS below), qEEG/ERP is considerably less expensive (by at least an order of magnitude) both in terms of capital equipment and in terms of per-use costs. Further, rather than collecting data in an expensive special purpose facility at a hospital or academic center, qEEG/ERP data can be collected in the field. These advantages most notably enable much larger sample sizes to enable better powered studies.

DTI. Diffusion tensor imaging (DTI), like fMRI, is based on magnetic resonance imaging (MRI), which itself is based on nuclear magnetic resonance (NMR), which is used widely in chemistry to resolve the structure of chemical compounds and has led to seven Nobel prizes (O'Donnell & Westin, 2011; Simpson et al., 2012; Taber et al., 2002). DTI can be viewed as a type of magnetic resonance imaging modality that enables resolution of neural microstructures, particularly subcortical white matter housing neural network circuits (O'Donnell & Westin, 2011; Taber et al., 2002). DTI uses stacked temporal arrays of weighted images processed through a diffusion tensor matrix (covariance matrix of a 3D Gaussian displacement distribution representing eigenvectors and eigenvalues) to directionally extract the relative rate of parallel anisotropic (directional) diffusion (via Brownian motion) of water along neuronal axons (O'Donnell & Westin, 2011; Taber et al., 2002). Tensors are simply algebraic objects that characterize multilinear relationships between groups of objects in vector space, and include scalars, vectors, and vector matrices (Kingsley, 2006). In DTI, first, tensors are measured, and then their eigenvectors and associated eigenvalues (eigenvalues and eigenvectors are described further in Chapter 3) are extracted from the tensor (Kingsley, 2006). The largest eigenvalue produces an eigenvector of the tensor to elucidate directionality along the axon and mapping of circuit fiber tracks (O'Donnell & Westin, 2011; Taber et al., 2002). Visualization of these maps is enabled, for example, via RGB color coding of individual tracks corresponding to their directionality, via glyphs, and via tractography (O'Donnell & Westin, 2011; Taber et al., 2002). Consequently, DTI is particularly useful for the study of neural circuits, such as dopaminergic neural projections. DTI has been used to study neurological disorders, such as Parkinson's disease (Schwarz et al., 2013), and DSM mental disorders, such as schizophrenia, including in combination with the PFC neurobiological proxy measure, the WCST (Kubicki et al., 2007),

autism (Lange et al., 2010), ADHD (Gagnon et al., 2022), and BPD (Sagarwala & Nasrallah, 2020).

MEG. Magnetoencephalography (MEG) is, like EEG, based on electromagnetism, with a focus on magnetic impulses rather than electrical impulses. MEG measures the magnetic activity generated by the electrical current gradients of, like EEG, pyramidal neuronal firing (Singh, 2014). However, capital and usage costs of MEG are an order of magnitude higher than EEG, reducing sample size per dollar for a study, requiring use of a specialized room and capital intensive equipment that cannot be used remotely (Singh, 2014). There are two advantages of MEG over EEG, however. First, magnetic fields travel from neurons to the surface of the scalp without distortion (unlike electrical impulses; Singh, 2014). Second, MEG has high spatial and very high temporal resolution (Singh, 2014). MEG is also often combined with MRI as magnetic source imaging (MSI) to improve structural sensitivity (Singh, 2014). Functionally, MEG and fMRI have been used in concert as well (Leonardelli & Fairhall, 2022). Magnetic field detection is enabled via use of either one or both of magnetometers (which are most sensitive to deep brain signals and competing magnetic waves) and axial and planer gradiometers (which optimally filter out magnetic noise; Singh, 2014). MEG has been used in RDoC studies to identify high gamma oscillations as biomarkers for ADHD using both self-report and laboratory behavioral neuropsychological measures (Dor-Ziderman et al., 2021), auditory evoked response biomarkers for ASD (Roberts et al., 2021), stimulation states in schizophrenia (Bai et al., 2023), including in combination with EEG (Gjini et al., 2020), and to identify neurobiological endophenotypes and biomarkers in combination with neuropsychological laboratory behavioral measures in BPD (Safar et al., 2019).

PET. Positron emission topography (PET) is a nuclear medicine method (i.e., requiring use of radioactive isotope tracers) that uses the rate of consumption of radiolabeled glucose analogs (18-fluorodeoxyglucose [FDG]) by the brain as a proxy for neuroanatomical brain activity (Berger, 2003; Muehllehner & Karp, 2006). The radioisotope emits a positron which collides with an electron in neuronal tissue to produce two gamma photons (Berger, 2003; Muehllehner & Karp, 2006). Scintillation detectors pick up the photons to produce a signal (Berger, 2003; Muehllehner & Karp, 2006). PET can also be used to track oxygen consumption and neurotransmitters, such as dopamine (Berger, 2003; Muehllehner & Karp, 2006). PET has been used to study dopamine (via the D1 receptors) in the ACC, dlPFC, and OFC in ADHD (Yokohura et al, 2021), for identifying biomarkers and endophenotypes in ASD including dopaminergic systems (Tan et al., 2022), to study the function of presynaptic striatal dopaminergic D2 and D3 receptors in schizophrenia (Vyas et al., 2010), and amygdala and PFC circuits in BPD (Kola et al., 2020).

SPECT. Brain perfusion single-photon emission computed tomography (SPECT), is a tissue localized nuclear imaging method that uses radioactive tracers (isotopes/probes) perfused into brain tissue that are then taken up by gamma detectors that transform radioactive traces into three dimensional images of functionally specific neuroanatomical loci (Santra & Kumar, 2014; Yandrapalli & Puckett, 2022). A common isotope for brain perfusion SPECT is technetium-99m (Tc) linked to hexamethylpropyleneamine oxime (HMPAO) perfused as a metabolic substrate by brain tissue, enabling localization of task dependent brain activity (Santra & Kumar, 2014; Yandrapalli & Puckett, 2022). Brain perfusion SPECT has been used to identify neuroanatomical loci as biomarkers for ADHD, schizophrenia, and ASD for example (Amen et al., 2021; Santra

& Kumar, 2014). For a list of studies that have used SPECT for ADHD, schizophrenia, and ASD see Santra and Kumar (2014).

fNIRS. Functional near-infrared spectroscopy (fNIRS) is a neuroimaging method that focuses on detection of modulation of oxygenated hemoglobin (oxyhemoglobin and deoxyhemoglobin like fMRI) in the brain (Chen et al., 2020; Wu et al., 2023). Unlike fMRI, fNIRS does not require a large magnetic scanner and measures oxyhemoglobin and deoxyhemoglobin separately (rather than as a ratio as with fMRI) and directly (fMRI uses BOLD response as a proxy; Chen et al., 2020). fNIRS is based on infrared light wavelength detection of light differentially absorbed by the two hemoglobin chromophores (Chen et al., 2020). fNIRS is far cheaper and less invasive and has far superior temporal resolution than fMRI although not as good temporal resolution as qEEG/ERP (Wilcox & Biondi, 2015). However, it has better spatial resolution (1-2 cm) than qEEG/ERP, but poorer than fMRI (Wilcox & Biondi, 2015) and eLORETA. fNIRS is also portable like qEEG/ERP, although more expensive to use (Mazzoni et al., 2019; Wilcox & Biondi, 2015). fNIRS has been used to study BRI in ADHD in conjunction with neuropsychological measures of BRI including the Stroop, go/no-go (GNG), and stop signal tasks (SST) associated with neural activity in the dlPFC and rIFG (Junior et al., 2023; Shin et al., 2023; Wu et al., 2023), to study PFC activity for BRI in ASD in combination with neuropsychological measures (Mazzoni et al., 2019), to identify PFC related biomarkers (and endophenotypes) for schizophrenia (Koike et al., 2013), and PFC activation in combination with the go/no-go task in BPD patients (Ruocco et al., 2021).

Table 8*Select Neuroimaging Methods*

Method	Spatial Res.	Tmporal Res.	Cost	Invasive	Portable	BRI Application	Primary Advantage
fMRI	1-3mm	1-2s	High	No	No	Brain Regions	High spatial res.
qEEG/ERP	1-2cm	1ms	Low	No	Yes	Neural circuits	High temporal res.
DTI	1-2mm	1-2s	High	No	No	White matter	Tract mapping
MEG	2-3mm	<1ms	Very High	No	No	Circuits/ regions	Both resolutions
PET	4-6mm	30-60s	High	Yes*	No	Neurotrans.	Neurochem.
SPECT	6-8mm	60s	Mod	Yes*	No	Blood Flow	Clinical Utility
fNIRS	1-2cm	100ms	Low	No	Yes	PFC Activity	Portable/ Inexpensive

Note: Tmporal res. = temporal resolution. Neurotrans = neurotransmitters, Neurochem = neurochemistry.

*Radiotracer

Neurobiological Endophenotypes Via Neuroimaging and Neuropsychological

Endophenotypes. As stated previously, the endophenotype hypothesis posits that the closer an endophenotype is to its genetic correlate (genotype) the stronger the association and the fewer

risk alleles implicated. Neurobiological endophenotypes are very close to their underlying genotypes. For example, certain dopaminergic alleles (e.g., DRD4-7R) implicated in behavioral phenotypes (e.g., ADHD) are often over expressed in certain brain regions (implicating fMRI measured endophenotypes) and brain circuits (implicating ERP component endophenotypes). Two ERP components (i.e., N2[N200]/P3[P300]) are discussed in detail later in this chapter, both individually and as a waveform complex. The above neurobiological endophenotypes are often measured while a subject performs a neuropsychological (laboratory behavioral) task measure to associate the neurobiological endophenotype with a psychological construct in neurotypical populations or in clinical populations of behavioral phenotypes (mental disorders). Neuropsychological endophenotypes are discussed next.

Neuropsychological Endophenotypes

Neuropsychological correlates (endophenotypes) related to executive functions (EF), impulsivity, and behavioral response inhibition (BRI) in the literature are measured using various psychometric and laboratory behavioral instruments. These include, among others, self-report measures, such as the Barratt Impulsiveness Scale (BIS-11) and UPPS-P impulsive behavior scale, and laboratory behavioral measures, such as the Iowa gambling task, flanker task, Simon task, Stroop task, Conners continuous performance test (CCPT), antisaccade task, go/no-go task (GNG), stop-signal task (SST), and the Wisconsin card sorting test (WCST, Afonso et al., 2021; Bohon et al., 2020; Cogden, 2008; Cogden et al., 2014; Friedman & Miyake, 2004; Korolczuk et al., 2018; MacKillop et al., 2016; Menkes et al., 2022; Miyake et al., 2000; Raud et al., 2020; Schachar et al., 2007; Sebastian et al., 2013; Shi et al., 2020; Skippen et al., 2020; Sperl et al., 2021; Stahl et al., 2014; Wessel, 2017; Zagarra-Valdivia & Chino Lilca, 2019).

As discussed previously and illustrated later, over the years, the research literature has tended to treat the above psychometric and laboratory behavioral measures as essentially indifferent to measurement of EF, impulsivity, or BRI. Reasons for this include the assumption that impulsivity and BRI are unitary constructs and that facets of these constructs can be equally measured across instruments. Even in cases where the literature has recognized that different facets of impulsivity and BRI map better to different instruments, there has been disagreement. For example, some authors (e.g., Kuntsi et al., 2001) argued that the stop-signal task (SST) best measures prepotent response inhibition, while others argued that it was the best measure of what this study refers to as prepotent response extinction (inhibition of an on-going response, e.g., Crosbie et al., 2008). While the literature has evolved to support that the SST best measures an ongoing response and that different measures measure different facets of BRI (e.g., Korolczuk et al., 2018; MacKillop et al., 2016), there are still many, more recent, studies that do not make such distinctions or still confuse them (e.g., Afonso et al., 2021; Ettinger et al., 2018).

Progress in the Literature and the Generic Model

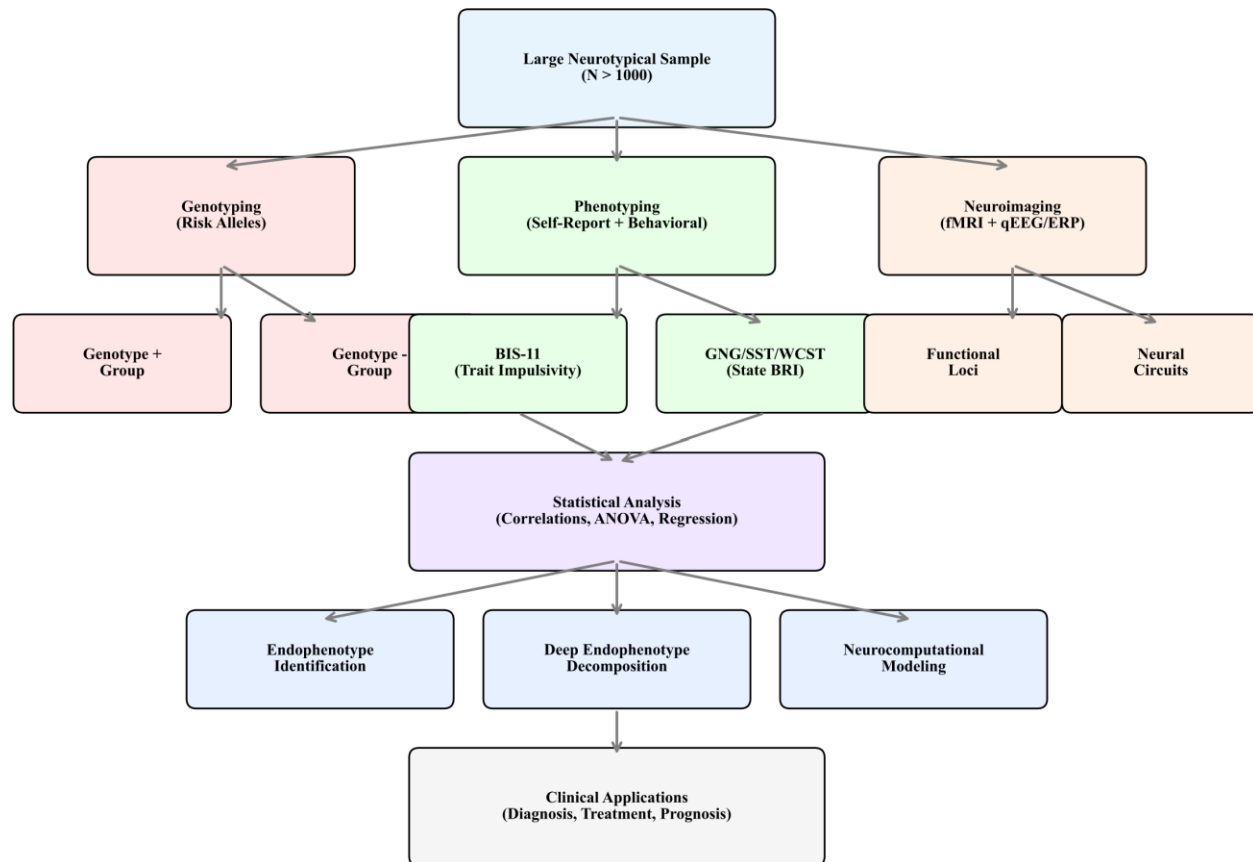
Below is a synthesis of the above categorical discussions regarding a plurality of constructs and measures that can comprise endophenotypes in their own right or comprise a deep endophenotype. They are discussed in the context of the developing endophenotype literature that combines measures. Before the development of the BRI endophenotype literature is discussed in detail, a generic example (the generic model) of a fully integrated and synthesized study is described to provide an aspirational design for a comprehensive study that is a natural evolution of the BRI endophenotype literature. One aim of this study was to provide validated endophenotypes and deep endophenotypes to be incorporated in such a comprehensive study to improve and better discriminate study outcomes. An additional aim is to use such validated

endophenotypes in AI enabled neurocomputational mechanistic, predictive, and clustering models of impulsivity, BRI, or disease models (digital twins) of certain DSM behavioral phenotypes, including for the purpose of informing differential diagnosis and treatment. Neurocomputational approaches are discussed in the last section of this chapter.

Example of a Generic Model Study

As suggested above, neurobiological measures are often combined with neuropsychological measures to identify neurobiological correlates of psychological constructs, such as impulsivity and BRI, and of behavioral phenotypes (DSM mental disorders). In endophenotype research under the RDoC, genetic correlates (risk alleles) of psychological constructs comprising endophenotypes and behavioral phenotypes are often of ultimate interest. Therefore, ultimately, combination studies aim to connect psychiatric and behavioral genetics to neuropsychological studies. Arguably, such studies connect the RDoC to the DSM.

To consolidate the discussion of the literature above and help frame discussion of the progress in the literature below, following is a general generic model, informed by the same literature, of a fulsome endophenotype candidate gene research study for BRI in a non-clinical population also tied to one or more behavioral phenotypes. While this is a complex example, with many latent, direct, confounding, and correlational variables, many details necessary for an operational exemplary study (e.g., details of quantitative design, specific variables studied, and statistical analysis) are ignored to simplify an otherwise complex concept. Figure 5 illustrates the Generic Model described below.

Figure 5*Generic Model for Comprehensive RDoC Endophenotype Study Design*

Ex-Post Facto Control and Treatment Groups of a Generic Model. First, assuming a regime where the RDoC again permits gene level units of analysis, a large sample of neurotypical adults is genotyped for one or more risk alleles of interest (e.g., DRD4-7R as a candidate gene or a panel of polygenic risk alleles) that have been implicated in BRI and one or more behavioral phenotypes (e.g., ADHD, ASD, schizophrenia, BPD). Genotyped subjects are then divided into genotype positive treatment groups (they have the risk allele) and genotype negative control groups (they have another allele of the same gene).

Neuropsychological Measurements for a Generic Model. Second, each study participant is administered a battery of neuropsychological instruments: (a) a self-report measure focused on impulsivity and BRI (e.g., BIS-11) and self-report measures focused behavioral phenotypes (e.g., the Minnesota Multiphasic Personality Inventory-2 [MMPI-2], Millon Clinical Multiaxial Inventory [MCMI-IV], and Diagnostic Interview for Borderlines [DIB-R]), and (b) laboratory behavioral measures focused on BRI (e.g., GNG, SST, WCST). A given study can exclude genotyping of candidate genes to reduce cross correlations (or in line with the current RDoC template), in which case ex post facto independent variable grouping can be based on self-report measures, such as the BIS-11 (as is the case of this study), preserving the transdiagnostic perspective of the RDoC.

Neuroimaging Measurements for a Generic Model. Third, during administration of the neuropsychological measures, subjects undergo (simultaneously or serially) fMRI and qEEG/ERP (combined with eLORETA) to map tasks performed for laboratory behavioral measures to neuroanatomical loci and neural network circuits.

Synthesis of Measures for a Generic Model. The BIS-11 self-report measure would identify trait impulsivity (including trait motor impulsivity) in the two groups. The MMPI-2 and MCMI-IV self-report measures would identify or confirm possible co-occurring or comorbid psychopathology (behavioral phenotypes) and clinical (pathology) and sub-clinical (trait) scales or other psychological constructs related to psychopathology (e.g., mania, hysteria, masochism). The DIB-R could be used to confirm a BPD profile suggested by the MMPI-2 or MCMI-IV or diagnosis from a clinical record. The neuropsychological measures would identify deficiencies in state impulsivity and BRI, including facets of BRI. FMRI would associate task measures of the neuropsychological instruments with functional brain locations. QEEG/ERP with eLORETA

would associate those same measures with activity of brain circuits via putative neurophysiological endophenotypes associated with BRI, such as the N2 (N200) or P3 (P300) ERP component or the N2/P3 complex waveform signature.

RDoC Endophenotypes and Units of Measure for a Generic Model. The above example would yield numerous possible neurobiological, neurophysiological, and neuropsychological endophenotypes related to the risk allele or alleles of interest and one or more behavioral phenotypes (e.g., BPD and its comorbidities) or trait measures. As noted in the RDoC section of this chapter, from an RDoC perspective, endophenotypes occur along a scale agnostic and transdiagnostic continuum. For a candidate gene study, one question for such a study would relate to the identification of the best candidate endophenotype. A key aspect of the above example of a generic model is that the effect size of association between genotype and behavioral phenotype relies, in part, on errors and sensitivity of measurement (units of measure) of numerous latent variables. Indeed, one can argue that much of the failure of RDoC endophenotype research arises from issues with the measures used (units of analysis or measure) and with identification of appropriate candidate endophenotypes along the continuum of those measures. Certainly, improving sensitivity, signal-to-noise ratios, and spatiotemporal resolution for the neurobiological measures are always goals. But the validity (e.g., face, construct, content, and criterion validity) of neuropsychological instruments is also critical.

Discriminating RDoC Units of Measure. The RDoC continuum includes measurement of facets of broader multidimensional constructs that may more strongly associate with certain risk alleles and neurobiological correlates, and that may better differentially associate with individual behavioral phenotypes. If certain neuropsychological measures (scales and subscales) can be better discriminate psychological constructs at one level, and facets of those constructs at

another level, they (scales and subscales) may be strong candidate endophenotypes in their own right or may better inform other candidate endophenotypes (e.g., N2/P3 complex).

The literature discussed above and below has improved the construct validity of neuropsychological instruments by identifying particular instruments best suited to particular constructs. But it has done far less as to identify instruments scales and subscales that dimensionalize those constructs. Consequently, if one can improve the construct validity of a neuropsychological instrument in the context of its ability to measure a facet of a broader construct, even if that compromises its content validity on the broader construct, it may be possible to better discriminate the genetic liability of the facet and improve its candidate endophenotype status. Such was one key goal of this study. With the above in mind, the progress and current state of the literature discussed next.

Studies Combining Neurobiological and Neuropsychological Correlates

The discussion below is primarily focused on literature over the past five years, but older studies are included that are important to illustrate the development of the research literature. The progression of the literature begins with the first connection between psychiatric genetic and neuropsychological studies and iterative addition of additional units of measure until illustration of studies most resembling the generic study discussed in the previous section.

Two seminal studies were among the first to combine psychiatric and behavioral genetics studies with neuropsychological studies (Kuntsi & Stevenson, 2001; Kuntsi et al., 2001). The authors studied risk alleles (genetic correlates) of ADHD via its hyperactivity symptom criterion. Included among neuropsychological measures was the stop-signal task (SST). The aim of the studies were to identify the genetic liability of neuropsychological measures implicated in ADHD through hyperactivity. However, the authors did not use the SST to do the same as to

BRI, instead treating it as a covariate, not the focus of study. Consequently, the authors did not identify BRI as a candidate endophenotype. Indeed, the authors did not refer to endophenotypes at all. In these studies, hyperactivity would be a candidate latent endophenotype with a corresponding operational endophenotype in the form of a neuropsychological measure.

As previously discussed, the psychiatric and behavioral genetics literature conducted genome wide association (GWAS), gene linkage, twin, and candidate gene studies to study the genetic liability of behavioral phenotypes. Other studies focused on neurobiological and neuropsychological correlates of behavioral phenotypes (eventually referring to endophenotypes proper) using neuroimaging, or neurophysiological, and neuropsychological measures. More recent studies have combined some or all of the above types of studies into single integrated studies to identify candidate endophenotypes that start to resemble the model generic example above—that is to say, connecting a genetic correlate (risk allele) to a neurobiological correlate (fMRI enabled brain region [functional loci] or qEEG ERP component or waveform complex), which is in turn associated with a neuropsychological correlate (task measure or DSM agnostic psychological construct), and, ultimately, to a behavioral phenotype (DSM mental disorder). This progression is discussed below along with examples of the gaps and problems in the literature discussed above, including failing to dimensionalize psychological constructs and their facets and confounding their measurement.

In a seminal study, Miyake et al. (2000) investigated EF and facets of BRI using neuropsychological instruments including the SST and WCST in a non-clinical sample. While the authors concluded the WCST discriminated inhibition and set shifting, they confounded other neuropsychological measures. Friedman and Miyake (2004) studied the latent variable facets of BRI in a non-clinical sample using antisaccade and Stroop tasks and the SST. Again, as with

many studies around that time, the authors concluded no material discrimination between interference control and prepotent response inhibition but did not discriminate between tasks measures as to individual facets.

Congdon (2008) studied alleles associated with BRI using fMRI (to identify neurobiological correlates) while non-clinical subjects (divided into genotype positive and genotype negative groups) underwent GNG and SST (neuropsychological correlates to tie neurobiological correlates to psychological constructs). The author noted that a lack of neurotypical populations and overabundance of clinical populations in the literature confounded dimensional measures of BRI with categorical measures of DSM disorders.

Sebastian et al. (2013) used the Simon task, GNG, and SST using fMRI in a non-clinical sample, concluding that GNG and SST are modulated by distinct neurotransmitter systems and implicated the right inferior frontal cortex (rIFC) in both prepotent response inhibition and prepotent response extinction (action cancelation). Shahaf and Pratt (2013) used qEEG/ERP to identify neurophysiological correlates of BRI using the GNG as the neuropsychological task measure in ADHD patients (the behavioral phenotype). Braunstein (2014) used qEEG/ERP and a neuropsychological measure of attention to study neural activity in the anterior cingulate cortex (ACC, a latent neurobiological correlate) in relation to deficient engagement of executive functions. As discussed previously, inattention, hyperactivity, and impulsivity are seminal to ADHD.

MacKillop et al. (2016) studied latent variables comprising facets of impulsivity using numerous neuropsychological self-report measures, including the BIS-11, and laboratory behavioral measures, including the GNG and SST in a non-clinical sample. The three facets

identified as orthogonal in their study, map onto prepotent response inhibition, cognitive impulsivity, and trait impulsivity (MacKillop et al., 2016).

Bhaijiwala (2016) studied neurobiological correlates of BRI as represented by the SST and measured using fMRI. However, this author studied a clinical population, ADHD, and further explored the concept that BRI is further divided into different facets that can be more directly characterized in terms of their neurobiological correlates. This focused on a developing problem in the literature, the ability of certain measures of a putative endophenotype, such as BRI via the SST, to more tightly map to their neurobiological (including genetic) correlates. Bhaijiwala (2016) framed the problem in the literature by parsing studies of different aspects of above generic model example of a fulsome study, suggesting studies that combine these elements. These included behavioral phenotypes, such as ADHD (Asherson et al., 2007), the psychological construct of BRI (Verbruggen & Logan, 2009), sub-facets of BRI (Chevrier et al., 2007; Schachar et al., 2007), and the choice of the SST as the ideal neuropsychological measure of behavioral response inhibition (Aron & Poldrak, 2005).

Ettinger et al. (2018) identified neuropsychological endophenotypes of two facets of BRI (prepotent response inhibition and interference control) in schizophrenia patients that included risk allele genotyping and employed numerous neuropsychological operational measures (antisaccade task, Stroop task, go/no-go task, stop-signal task, and Simon task). The authors concluded that the antisaccade task best measured prepotent response inhibition. In contrast, Korolczuk et al. (2018) studied the three facets of BRI described previously using the Simon task, flanker task, Stroop task, and SST in non-clinical subjects. These authors concluded that the Simon task best measured interference control and SST best measured inhibition of an ongoing task (prepotent response extinction).

Zegarra-Valdivia and Chino Vilca (2019) used the WCST, and other neuropsychological measures, to study a clinical sample of patients with borderline personality disorder (BPD) to identify BPD executive function endophenotypes and neurobiological correlates. They relied on WCST's recognition as a key proxy for deficits in the PFC, described previously as central to executive function. The study included as exclusion criteria, common comorbidities with BPD, which, as mentioned above in the section on BPD, does not represent natural patient populations.

Bong et al. (2020) studied anxiety patients using qEEG/ERP to study EF deficits with the P300 ERP component as a candidate endophenotype of EF deficits (the latent variables). The authors explicitly invoked the RDoC, noting that qEEG/ERP was superior to fMRI for RDoC studies, since the RDoC focuses on brain circuits (dynamic network analysis paradigm). The significance of the P300 ERP component as a putative endophenotype of BRI had, by the time of Bong et al., (2020), become a key target of the literature as discussed in the next section.

Skippen et al. (2020) studied neurobiological correlates of BRI in a non-clinical sample using the SST with qEEG/ERP with the N1/P3 ERP waveform complex as a candidate endophenotype. Raud et al. (2020) used both the GNG and SST on a non-clinical sample under qEEG/ERP via the P3 (P300) ERP component. Raud et al. (2020) concluded that the GNG and SST rely on different neural mechanisms, suggesting they may serve as differential candidate endophenotypes. Raud et al. (2020) further noted that the literature's characterization of the GNG and SST as interchangeable measures of a unitary construct of BRI (and impulsivity by proxy) is likely incorrect.

Sperl et al. (2021) used qEEG/ERP in a non-clinical sample while performing the SST and flanker task to characterize the P300 (P3) ERP component as a candidate endophenotype. The authors concluded that selection of the neuropsychological measure is critical to

dimensionalize facets of BRI (Sperl et al., 2021). The authors further concluded that response inhibition is related to motor processes and interference control to cognitive process (Sperl et al., 2021). However, Sperl et al. (2021) confounded the facets of BRI, in part, due to confounding their measures.

Menkes et al. (2022) sought to discriminate BRI and its neurobiological correlates between schizophrenia and bipolar disorder using qEEG/ERP while 146 participants (each a clinical group and a healthy control [HC] group) performed the affective GNG. The authors focused on the N2/P3 (N200/P300) waveform complex as a putative endophenotype using emotive facial expression as a differentiating marker (Menkes et al., 2022). The authors noted that most GNG studies for BRI focus on higher dimensional accuracy and commission errors, and sought to decompose the accuracy measure to discriminate its facets of sensitivity and response bias (Menkes et al., 2022). Their study is one of the first to begin to take a decomposition approach to measures of BRI. This study aims to take the next step in that evolution.

Cane et al. (2023) studied BRI subconstructs of RDoC's cognitive control domain in clinical samples of borderline personality disorder (BPD) and major depressive disorder (MDD) where deficits in BRI are dimensional and transdiagnostic. The authors noted, for example, that prior studies indicated that BPD patients have more commission errors and lower P3 amplitudes in GNG qEEG/ERP studies (Cane et al., 2023). In their study, the authors used the GNG as a proxy for BRI (without decomposition) in combination with fMRI to identify differential neural activation patterns between BPD and MDD in the context of BRI (Cane et al., 2023). They studied 21 controls, 16 patients with MDD and 18 with BPD comorbid with MDD (Cane et al., 2023). Although the authors identified distinct differences in commission errors of the GNG

neuropsychological measure, they did not identify significant differences in the neurobiological fMRI functional imaging measure, perhaps, suggesting the limitations of fMRI vs. qEEG/ERP to differentiate neural activation in these groups (Cane et al., 2023).

Hong et al. (2024) used the GNG in combination with qEEG/ERP focused on the N2(N200)/P3(P300) waveform complex to study prepotent response inhibition in a schizophrenia clinical population. The authors compared behavioral outputs from the GNG between 31 healthy controls and 29 patients and N2/P3 ERP amplitudes (Hong et al., 2024). Results indicated more frequent error responses to no-go stimuli and reduced P3 amplitude in clinical samples (Hong et al., 2024). The study decomposed the three facets of BRI by noting that results suggested deficits among schizophrenia clinical samples in prepotent response inhibition and the P3 component, but not interference control and the P2 component (Hong et al., 2024). Krakowski et al. (2024) studied the neural correlates of BRI in schizophrenia using fMRI while study subjects undertook the GNG. The authors studied 44 schizophrenia patients and 40 controls and observed that schizophrenia patients had higher commission errors (CE) on the GNG than healthy controls (Krakowski et al., 2024). fMRI results implicated higher activation (failure to deactivate) in the default mode network (DMN) in schizophrenia patients, particularly the insula, precuneus, parahippocampus, and rostral anterior cingulate (Krakowski et al., 2024). Although the literature implicates prepotent response inhibition and BRI descriptions by these authors are consistent with that facet, the authors did not make facet distinctions per se.

Saracaydin et al. (2025) studied the neural correlates of BRI in ADHD co-occurring or comorbid with disruptive behavioral disorders (DBDs), such as conduct disorder (CD) and oppositional defiant disorder (ODD), using fMRI and performance based SST (this study uses a performance based SST virtually identical to that of the authors' study). The authors took an

RDoC informed dimensional approach and administered the SST while undergoing fMRI to in 35 children and adolescents and 31 age-matched controls (Saracaydin et al., 2025). They determined that deficient BRI (a failure to extinguish the go signal upon hearing the stop signal) implicated the right frontal and left parietal loci and successful inhibition implicated the left lateral occipital cortex activation in a behavioral phenotype orthogonally dependent manner (Saracaydin et al., 2025). The authors did not, however, distinguish the facets of BRI with SST scores and fMRI results. For example, while the authors noted that the default mode network (DMN; here, its bilateral precunei hub) was implicated using language that suggests the interference control facet of BRI (in contrast to Krakowski et al. above that suggests prepotent response inhibition in the context of DMN activation), the SST best measures the action cancellation (prepotent response extinction) and not interference control, so it is difficult to reconcile the neural correlates (including the DMN) at the facet or component level for BRI since, as discussed previously, interference control implicates different neural correlates than prepotent response inhibition or prepotent response extinction within BRI.

The N2/P3 Neurobiological/Neurophysiological Endophenotype

As the endophenotype literature for BRI related behavioral phenotypes has evolved, key neurobiological endophenotypes comprising neurophysiological measures have emerged in addition to endophenotypes comprising laboratory behavioral measures (e.g., GNG, SST, CCPT, flanker task), each being operationalized embodiments of the latent variable endophenotype of BRI and its facets. These include ERP components from qEEG/ERP studies. Two ERP components in particular have been implicated in BRI, the N2 (N200) and P3 (P300) components (Anokhin et al., 2017; Dück et al., 2023).

In qEEG/ERP studies that use the GNG behavioral task measure as a neuropsychological functional measure, for example, the N2 component appears between 200 milliseconds and 270 milliseconds after the no-go stimulus in trials where prepotency is successfully inhibited (Anokhin et al., 2017; Dück et al., 2023). It is posited that N2 amplitude is larger when there is a conflict between the primed prepotent response and its inhibition, and inhibition wins the conflict (Anokhin et al., 2017; Enriquez-Geppert et al., 2010; Gholamipourbarogh et al., 2024; Groom & Cragg, 2015). Neurobiologically, when source localization is used (such as LORETA with qEEG/ERP or fMRI in combination with qEEG/ERP) studies have implicated the anterior cingulate cortex (ACC; Anokhin et al., 2017).

A second ERP component, the P3 (P300), is also associated with a successful no-go response and appears between 250 milliseconds and 500 milliseconds after successful inhibition in GNG tasks (Anokhin et al., 2017; Dück et al., 2023). It has also been used in studies using the SST (Dück et al., 2023; Waller et al., 2021). It is most often associated with proper engagement of the prefrontal cortical circuitry involved in executive functions (Anokhin et al., 2017; Groom & Cragg, 2015). As compared to the P2, which appears at conflict onset (go vs. no-go in the presence of a no-go stimulus), the P3 appears on successful BRI (motor inhibition; Anokhin et al., 2017; Enriquez-Geppert et al., 2010; Gholamipourbarogh et al., 2024; Groom & Cragg, 2015; Hong et al., 2024; Waller et al., 2021). Neurobiologically, source localization methods have implicated the ACC, dfPLC, and pre-supplementary motor area (pre-SMA) cortical regions as activated on evoked P3 (Anokhin et al., 2017). As compared to the N2 component, the P3 component has been more consistently associated with deficiencies in BRI and associated behavioral phenotypes including several of the DSM disorders implicating impulsivity described in this chapter (Anokhin et al., 2017; Gholamipourbarogh et al., 2023; Groom & Cragg, 2015).

In addition to P3 amplitude, P3 latency (or onset shifts in latency) has also been implicated as a candidate endophenotype for BRI in conjunction with the SSRT outcome variable of the SST (Dück et al., 2023; Huster et al., 2020). However, P3 latency correlates with N2 latency in the SSRT of the SST (Huster et al., 2020). Research on both N2 and P3 amplitude and latency suggests that study of the N2/P3 waveform complex as a candidate endophenotype over individual ERP components may be more elucidative in BRI related RDoC endophenotype research.

Both the N2 and P3 ERP components have been shown to be highly heritable in both adults (as much as 60%; Anokhin et al., 2004) and in adolescents (as much as 63%; Anokhin et al., 2017). The N2/P3 (N200/P300) complex (or individually) therefore is a putative endophenotype of BRI and related behavioral phenotypes operationalized via top level and outcome variables of the GNG and SST (each also putative endophenotypes). For example, Huster et al. (2011) combined qEEG/ERP/fMRI studies with the SST and identified neuroanatomical functional loci associated with BRI including the ACC, pre-SMA, and anterior insula. However, Huster et al. (2011) did not distinguish what facet of BRI the SST was measuring, prepotent response inhibition or prepotent response extinction. Interestingly, the N2/P3 waveform endophenotype of BRI has a developmental dimension. As an individual ages from childhood to adulthood, N2 amplitude decreases while P3 amplitude increases (Anokhin et al., 2017). This indicates lower conflict as prefrontal executive function cognitive control loci and circuits mature in their efficacy (Anokhin et al., 2017). Consequently, the P3 (P300) ERP component is often the key component for BRI, as a decreased P3 amplitude vs controls in children and adults relative to age matched controls indicates a deficiency in BRI (i.e., impulsivity; Anokhin et al., 2017; Cheung et al., 2015; Hong et al., 2024; Waller et al., 2021).

No qEEG/ERP studies to date, however, have examined N2/P3 amplitude or relative latencies using select outcome variables separately of each of the GNG, SST, or the WCST in groups bifurcated by trait motor impulsivity subscales of the BIS-11. Enriquez-Geppert et al. (2010) for example, used a blended SST/GNG behavioral task version that did not distinguish instrument outcome variables and trait dimensions in this manner. This study aimed to identify neuropsychological and neurobiological (by proxy) endophenotypes related to these subscales and outcome variables that can then be incorporated into such studies to further and more discriminately characterize P2/P3 putative endophenotypes of BRI and its upstream implicated behavioral phenotypes. Such discrimination can be used to better inform studies of either N2 or P3 ERP components or the N2/P3 waveform complex in similar studies of behavioral phenotypes. For example, as discussed previously in the section in this chapter relating to endophenotype typing and decomposition (deep endophenotyping), Ford (2014) suggested to decompose the P3 to better enable its discrimination and association with candidate genes for schizophrenia (candidate SNP alleles), which, due to gaps in the BRI endophenotype literature, has not been possible. This study provided one opportunity to inform a more complex study similar to the model study in light of Ford (2014) with the decomposed endophenotypes of this study.

Research Literature Illustrating Key Concepts and Gaps

Several authors have identified key conceptual gaps and problems in the literature. Lenartowicz et al. (2010) made a critical ontological argument regarding EF, including BRI, fundamental to the premise of cognitive neuroscience, and thus behavioral neuroscience—that is, to map cognitive functions (cognitions), and thus behavior (motor actions), onto their neural substrates (neurobiological correlates)—that each cognitive and behavioral construct, such as

BRI (i.e., a candidate endophenotype) and each uniquely measurable facet of that construct, should map onto a unique neural substrate (neurobiological correlate). However, McKenna et al. (2017) conducted a meta-analysis that concluded that neurobiological correlates rely on the structure of neuropsychological tasks that implicate different systems (endophenotypes) that the literature does not distinguish. In combination, these different systems can comprise deep endophenotypes.

The above perspectives suggest that different neuropsychological instruments should measure distinct facets of broader constructs, such as prepotent response inhibition, on the one hand, and prepotent response extinction (response cancellation), on the other hand, as facets of the broader construct of BRI. At a higher scale, BRI, motor, attentional, and non-planning impulsivity, for example, map as facets of the broader construct of impulsivity where BRI and motor impulsivity are linked and mapped to unique neural substrates—that is, neurobiological correlates should map uniquely to differential endophenotypes, and in turn, cognate behavioral phenotypes. Again, endophenotype decomposition leads to deep endophenotypes.

With respect to genetic substrates mapping onto an endophenotype and its cognate behavioral phenotype, Fortgang et al. (2016) conducted an influential study that is an example of the above concept. Their study started with the construct of impulsivity as a candidate endophenotype for bipolar disorder, schizophrenia, and major depressive disorder. Then it focused on five lower order facets of impulsivity, including BRI and motor impulsivity, as measured by the SST. It treated these as differential candidate endophenotypes in probands and their twins (a twin study) to characterize heritability of each facet as loaded individually on each of, or across all of, the three behavioral phenotypes. The authors concluded that three facets, including motor inhibition, loaded on all three behavioral phenotypes as shared endophenotypes,

but not the SST measure associated with BRI. In other words, the authors did not, or could not, differentiate the SST measure as a candidate endophenotype for BRI or for other facets of impulsivity with respect to the studied behavioral phenotypes. This is due perhaps, in part, because Fortgang et al. (2016) did not further stratify facets of impulsivity that were putative candidate endophenotypes into their lower order facets that could be differentially distinguished by the SST, as the above concept suggests. Where, as previously described, the SST may best measure the second facet of BRI (i.e., prepotent response extinction), while Fortgang et al. (2016) applied the above concept, in line with the ontological argument of Lenartowicz et al. (2010), they arguably did not go far enough.

Development and Gaps in the Endophenotype Literature. As previously illustrated, research on psychopathology and its neurobiological correlates has historically been framed by the DSM's diagnostic categorical nosology. Such research aims to inform the etiology of individual mental disorders and their diagnosis and treatment (Sanislow et al., 2019). However, also as previously mentioned, many studies, such as candidate gene studies, demonstrate weak associations, at best, between candidate genes and downstream DSM psychopathology (behavioral phenotypes; Cuthbert & Morris, 2021; Sanislow et al., 2019). Several RDoC informed reasons help explain these limitations. First, DSM psychopathologies are based on categories of symptoms that define diagnosis, but their neurobiological correlates are not (Sanislow et al., 2019). Second, diagnostic categories are not exclusive, but inclusive and multifactorial, in that different individuals can meet diagnostic criteria by presenting different heterogenous combinations of symptoms, confounding poor associations between individual neurobiological correlates and behavioral phenotypes (Cuthbert & Morris, 2021). Further, many DSM framed studies select pure clinical samples, where most patients have comorbid DSM

diagnosis (Sanislow et al., 2019; Zegarra-Valdivia, 2019). This results in studies that often neither represent natural patient populations nor consider dynamic and complex transdiagnostic features of neurobiological correlates of psychopathology, such as Saracaydin et al. (2025) did above.

As described previously, the National Institutes of Mental Health (NIMH) attempted to address this through a conceptual framework, the Research Domain Criteria (RDoC; Sanislow et al., 2019). Again, the RDoC subscribes to the endophenotype hypothesis via a matrix of functional domains and constructs (behavioral systems) and neurobiological, neurophysiological, and neuropsychological units of analysis (measures, scales, dimensions, paradigms) comprising transdiagnostic intermediate phenotypes (endophenotypes), agnostic to behavioral phenotypes (Bong et al., 2020; Demetriou et al., 2019; Sanislow et al., 2019). For example, impulsivity appears in the subconstruct of response selection: inhibition/suppression, under the construct of cognitive control, under the cognitive systems domain of the RDoC matrix (Demetriou et al., 2019; NIMH, 2021).

However, nearly 50 years since the endophenotype concept was introduced to psychology (Gottesman & Gould, 2003), endophenotypes have fallen short of simplifying studies of links between genotype and behavioral phenotype and have been questioned as viable units of study (Jonas & Markon, 2014). Similarly, studies of the construct of impulsivity as a putative endophenotype have been so inconsistent or demonstrated weak or non-repeatable associations with genotypes or behavioral phenotypes as to suggest that impulsivity may not be a construct at all, let alone an appropriate candidate endophenotype (Stahl et al., 2014; Strickland & Johnson, 2021). However, the issue may not be a problem with the endophenotype concept or whether

impulsivity is a viable putative endophenotype, but a problem of scale (dimension) and of appropriate endophenotype selection and its method of measurement.

As previously mentioned, the research literature often treats impulsivity as unitary and assumes neuropsychological measures of impulsivity are indifferent (scale agnostic) to the dimensions (scales) they measure (Friedman & Miyake, 2004). More recently, it treats impulsivity facets (components) as unitary across scales (dimensions) of study as well as its measures (Ettinger et al., 2018; Raud et al., 2020; Stahl et al., 2014). Even the RDoC itself is not immune from confounding constructs and subconstructs and their measures. For example, the RDoC matrix confounds impulsivity with response selection and inhibition/suppression and suggests that measurements of impulsivity/inhibition include self-report and laboratory behavioral measures, without addressing impulsivity facets or which measures best measure those facets (NIMH, 2023). Indeed, a significant number of studies fail to make such distinctions, often mixing self-report measures with laboratory behavioral measures (Ettinger et al., 2018; Friedman & Miyake, 2004; Stahl et al., 2014). However, as previously stated, self-report and laboratory behavioral measures are poorly correlated in the literature (Cyders & Coskunpinar, 2011; Ellingson et al., 2018; Stahl et al., 2014). Further, these measures are used to study a plurality of definitions of impulsivity assumed unitary, ignoring the high dimensionality implied by such disparate definitions described in the section on impulsivity (Stahl et al., 2014).

Finally, impulsivity is affirmative behavior whereas inhibition implies the opposite, a means to keep impulsivity in check, yet deficits in BRI are often treated as synonymous with impulsivity in the literature (Stahl et al., 2014). The literature has slowly, if not inconsistently, acknowledged that impulsivity and its facets, are not unitary, and that different neuropsychological measures apply to different facets (Bhaijiwala, 2016; Eagle et al., 2008;

Ettinger et al., 2018; Friedman & Miyake, 2004; Korolczuk et al., 2018; MacKillop et al., 2016; Raud et al., 2020; Shi et al., 2020; Stahl et al., 2014; Tiego et al., 2018). Arguably, however, it has not gone far enough, and similar dimensionality problems of impulsivity facets (or of inhibition/impulse-control) have surfaced at lower scales of study, with many of the same problems as those at higher scales (Afonso et al., 2021; Ettinger et al., 2018; Friedman & Miyake, 2004; Raud et al., 2020; Skippen et al., 2020; Stahl et al., 2014).

Stahl et al. (2014) studied five factors (facets) of impulsivity in 198 adults using various neuropsychological self-report and laboratory behavioral measures. The authors concluded that the interference control and inhibition factors each comprised a plurality of facets (Stahl, et al., 2014). Further, they observed that what appear to be closely related and interchangeable task measures (neuropsychological endophenotypes) actually measure different orthogonal facets of impulsivity, which suggest that their neurobiological correlates (implicated genes, neural circuits, and functional brain regions) are distinct, supporting findings from prior studies and supported in latter studies (MacKillop et al., 2016; Sebastian et al., 2013; Stahl et al., 2014). Stahl et al. (2014) further note that lack of clearly defined facets (dimensions) of impulsivity and consensus on their measurement presents a gap in the literature that urgently needs to be filled. However, even with this advancement in the literature, these authors confounded impulsivity as affirmative behavior and inhibition as its regulator, including self-report measures for the former and laboratory behavioral measures for the latter. Many studies and researchers continue to confound neuropsychological and neurophysiological measures of facets of impulsivity or inhibition (Afonso et al., 2021; Bhajjiwala, 2016; Congdon et al., 2014; Eagle et al., 2008; Schachar, 2007; Sperl et al., 2021; Wang et al., 2016; Wilburtz et al., 2014). Indeed, among the

goals of the RDoC, are to better define the matrix constructs and their measures (differentiating and improving dimensionality etc., NIMH, 2023).

Thus, there remains numerous problem methodological gaps in the literature as well as empirical and knowledge gaps. First, lower order facets of inhibition are not consistently measured by not only distinct neuropsychological measures, but also subscales of those measures, to identify more suitable candidate endophenotypes via stronger links to neurobiological correlates and/or behavioral phenotype. Second, task measures do not consistently discriminate facets so measures of neurobiological and neurophysiological endophenotypes (e.g., fMRI and EEG) do not consistently and reliably differentially map those facets. Fourth, tasks do not consistently discriminate facets, so fail to consistently differentially map onto behavioral phenotypes, if at all. Fifth, an empirical and knowledge gap, the literature has failed to test (or discriminate) whether subscales of self-report measures are better correlated with subscales of laboratory behavioral measures than higher order scales (factors) are correlated between self-report and laboratory behavioral measures. This final gap ties to previously described poor correlation between self-report and laboratory behavioral measures in the literature (Barnhart & Beulow, 2017).

For example, genotype, fMRI, and qEEG/ERP studies have struggled to support each-other's findings and to discriminate specific genes, brain regions, or neural processes (neurobiological correlates) related to specific neuropsychological tasks, and, consequently, behavioral phenotypes (Bhaijiwala, 2016; Congdon, 2008). As facets of inhibition have been better mapped to specific neuropsychological measures, mapping to neurophysiological and neurobiological measures has also improved (Bong et al., 2020; Sperl et al., 2021). Using the RDoC framework, each unit of measure is a putative endophenotype and this process of better

discrimination (dimensionalization) may be termed RDoC latent variable endophenotype decomposition (deep endophenotyping), which was the focus and goal of this study.

The implications of this study on the development of the research literature discussed above is tied to the evolution of study complexity to the level of the RDoC generic model study discussed above. As the literature has bridged the gap between psychiatric and behavioral genetics and the DSM by combining RDoC units of measure (units of analysis) across scales of measure to study a plurality of constructs implicated in a plurality of heterogenic DSM behavioral phenotypes, each unit of measure (and their facets, features, and components) or construct (and all its sub-constructs, subtypes, and facets) can pleiotropically serve as a candidate endophenotype and comprise a deep endophenotype for any number of behavioral phenotypes. This results in a large number of multimodal (data from different units of measure, such as different behavioral and neuroimaging measures) dependent and independent variables, latent and observable, including (invoking NDST) variables that shift from independent to dependent and back again, along with an array of outcome variables and data (Gagnon et al., 2022; Sanislow et al., 2022). Further, decomposition of individual variables, by definition, increases their dimensionality, increasing variable and data density, which is computationally resource intensive (Gagnon et al., 2022; Tai et al., 2019).

While, as discussed below, one typically seeks to reduce dimensionality of data, rather than increase it, to improve computational efficiency, use of higher dimensional (decomposed) data can lead to better understood and segregated neurocomputational model inputs, which can improve model sensitivity and selectivity and outputs of neurocomputational models, and also improve downstream dimensional reduction techniques and feature extraction when using ensemble methods. Consequently, application of the techniques of computational neuroscience

and artificial intelligence (AI) can benefit from decomposed and validated endophenotypes, such as those of this study. These methods, include neurocomputational methods invoking NDST and using the tools of AI, including machine learning and deep learning, to help process, reduce, (de-dimensionalize), parse, cluster or stratify, and analyze high dimensional data from such decomposed and validated endophenotypes (Schnack, 2019; Tai et al., 2019). Such methods can also include development of neurocomputational mathematical models (digital twins) of dynamical systems comprising transdiagnostic psychological constructs and their endophenotypes and deep endophenotypes and of behavioral phenotypes. Such models depend on higher quality and better discriminated input variables, such as outcome measures from decomposed endophenotypes of this study. Discriminated inputs should lead to discriminated outputs. The neurocomputational modeling literature is discussed next.

Neurocomputational Applications and RDoC Studies

In 2017, Joshua Gordon, the then new director of the National Institute of Mental Health (NIMH), an institute of the National Institutes of Health (NIH), wrote an article on the future of the RDoC (Gordon, 2017). Consistent with the RDoC's behavioral neuroscience foundation, Dr. Gordon described the RDoC as "an effort to understand the connection between behavior (and disorders) and biology" (Gordon, 2017). He further described the RDoC consistent with the discussions in this chapter regarding the literature related to this study: "[t]ake behavior, break it down into its component parts, and study the psychobiological factors relating to these parts, from genes and molecules to neural circuits and behavior." (Gordon, 2017). Consistent with the RDoC's reliance on the endophenotype hypothesis, those component parts comprise endophenotypes, including decomposed endophenotypes comprising deep endphenotypes.

Dr. Gordon also noted an issue, discussed previously in this chapter with respect to RDoC's domain classification of impulsivity and BRI, that the current descriptions of those components in the RDoC matrix, as domains, constructs, and sub-constructs, are not necessarily optimally classified or even correctly constructed (Gordon, 2017). Dr. Gordon concluded that the future of the RDoC (the topic of his article) is to refine those domains, and the RDoC's transdiagnostic dimensions, through the use of neurocomputational approaches that can find hidden (latent) clusters of patterns in massive sets of high dimensional data from RDoC's scaling units of analysis, to construct behavioral domains of the RDoC from the bottom-up rather than from the top-down as, similar to the DSM, they were originally built (Gordon, 2017). To that end Dr. Gordon described "using computational techniques (clustering analysis or dimensional reduction techniques) to examine the underlying structure of behavioral performance across" the RDoC task paradigms (e.g., BIS-11, GNG, SST, WCST) to invoke a bottom-up domain construction (Gordon, 2017). Consequently, because a key goal of this study was to provide higher quality inputs (empirical and mathematical preprocessing features) in the form of decomposed endophenotypes for neurocomputational models of behavioral phenotypes (and psychological constructs), this chapter finishes with a description of neurocomputational applications and the neurocomputational literature related to impulsivity, BRI, and the four behavioral phenotypes discussed in this chapter. These neurocomputational applications include high dimensional data clustering methods, theory driven fitting methods, and atheoretical data driven feature extraction methods using AI (statistical machine learning and deep learning through multilayered artificial neural networks).

As discussed previously in this Chapter, NDST is implicit in the RDoC. Further, one goal of this study was to provide reductionist dimensional decomposition empirical and mathematical

preprocessing features (decomposed [deep] endophenotypes) for studies that develop high dimension neurocomputational models of impulsivity and BRI for specific behavioral phenotypes that take an emergent and wholistic NDST perspective. Indeed, this is a planned application of the outcome of this study. To repeat from the discussion in the NDST section of this chapter, a premise of this study was that decomposed endophenotypes (and deep endophenotypes) can be used in neurocomputational studies of BRI and of behavioral phenotypes. Again, better inputs result in better outputs and neurocomputational models of complex neurobiological systems require more precise segregation and dimensionalization (i.e., decomposition of low dimensional data to high dimensional data) of system elements so as to better understand their interactions.

While NDST was not selected for this study because it is already implicit in the RDoC, it is best applied directly in the context of neurocomputational studies that employ or study emergent complex neurobiological and behavioral systems and not reductionist elemental studies such as this study. Also, as discussed previously, NDSTs application to psychology and behavioral neuroscience requires substantial computing power, particularly with respect to neurocomputational modeling of high dimensional data (Sterratt et al., 2024).

Neurocomputational models implicate the field of computational neuroscience (discussed below), and the concept of high dimension (as high dimensional data) implicates the field of artificial intelligence (also discussed below), or more appropriately, the subfields of statistical machine learning (ML) and multilayered artificial neural networks (MLANN; i.e., deep learning; Anastasio, 2010; Sterratt et al., 2024). Because one goal of this study was to provide better empirical and mathematical preprocessing features (inputs) to neurocomputational studies, these concepts are first discussed below, followed by their application in studies of endophenotypes of

impulsivity and BRI and the behavioral phenotypes of ADHD, ASD, schizophrenia, and BPD.

Practically speaking, this is the field of computational and behavioral neuroscience.

Computational and Behavioral Neuroscience

Mathematical neuroscience is essentially theoretical neuroscience that uses complex mathematical and statistical models to formulate theoretical abstractions of dynamical neural network systems in the brain across spatiotemporal RDoC scales, from the molecular level, to the synapse, to the neuron, to neural circuits (projections), to entire neural network systems (Anderson, 2014; De Schutter, 2010; Khaleghi et al., 2022; Liu & Li, 2024; Mallot, 2013; Miller, 2018; Sanchez, 2021; Sterratt et al., 2024; Trappenberg, 2010). Computational neuroscience deploys computational algorithms (including via the use of AI machine learning and deep learning) to solve, validate, fit, and dynamically iterate these complex mathematical (including, e.g., NDST enabled cellular automata models) and statistical models in computer simulations, which can be representative of current states or predictive of future states (Anastasio, 2010; Anderson, 2014; De Schutter, 2010; Liu & Li, 2024; Mallot, 2013; Miller, 2018; Sanchez, 2021; Stephan et al., 2008; Sterratt et al., 2024; Trappenberg, 2010). These are often called neurocomputational models and can be descriptive of a neurobiological system (the what), explain mechanisms of operation of a neurobiological system (the how), and even help explain why a neurobiological system operates in a certain manner (the why; Anderson, 2014; Moustafa, 2018; Sanchez, 2021; Sterratt et al., 2024).

Neurocomputational models can also be divided into theory driven models and data driven (atheoretical) models (Pauli & Lockwood, 2023; Stephan & Mathys, 2014). Theory driven neurocomputational models (using reinforcement learning or Bayesian optimal fitting or Bayesian causal modeling [BCM], for example) can be used to understand mechanisms (Huys et

al., 2016; Khaleghi et al., 2022; Pauli & Lockwood, 2023; Stephan & Mathys, 2014). Data driven atheoretical approaches (using machine learning and deep learning) can be used to find hidden clusters (from data fed into the model with no hypothesis) to create predictive models to diagnose and treat psychiatric disease (Huys et al., 2016; Khaleghi et al., 2022; Pauli & Lockwood, 2023). Theory (hypothesis) driven models are used in the development of neurocomputational models of behavioral phenotypes (i.e., digital twins; Huys et al., 2016; Khaleghi et al., 2022; Pauli & Lockwood, 2023). Data driven atheoretical models are then used to inform the diagnosis, treatment, and prognosis of behavioral phenotypes (Huys et al., 2016; Khaleghi et al., 2022; Pauli & Lockwood, 2023). Atheoretical data driven neurocomputational models are also used to develop theories (hypothesis) that can then be used to populate theory driven models (Huys et al., 2016; Khaleghi et al., 2022; Pauli & Lockwood, 2023).

Computational and behavioral neuroscience concerns the development of neurocomputational models of the neurobiological substrates of behavior or of behavioral systems with a neurobiological nexus (Anderson, 2014; Florez, 2012; Moustafa, 2018; Wilson & Collins, 2019). The algorithms used in neurocomputational models, being computational operational embodiments of complex mathematical models, include the deterministic, chaotically deterministic, non-linear, and stochastic complex mathematics of NDST (see NDST section) and often employ statistical mathematical models (Bayesian or frequentist), using methods such as principal component analysis (PCA) and more esoteric methods, such as cellular automata (Anastasio, 2010; De Schutter, 2010; Liu & Li, 2024; Mallot, 2013; Petzschnner et al., 2017; Sanchez, 2021; Stephan & Mathys, 2014; Sterratt et al., 2024).

When neurocomputational algorithms are iterated recursively, are statistically trained with real neurobiological or behavioral data, or adapt based on iterative and recursive feedback

from dynamic local transformations or phase transitions of real neurobiological or behavioral data or evolving abstractions of that data, they deploy the tools of artificial intelligence (AI), namely statistical machine learning (ML), and deep learning that employs multilayered artificial neural network (ANN) algorithms (Anastasio, 2010; Anderson, 2014; De Schutter, 2010; Mallot, 2013; Pauli & Lockwood, 2023; Sanchez, 2021; Sterratt et al., 2024; Subramanian et al., 2022). Multilayered ANN's are particularly suited to characterize, model, fit, and predict non-linear dynamical systems, the application of AI to NDST, including multilayered feedforward neural networks (MNNs) and multilayered perceptron neural networks (MLPs) that use arrays of latent variables (impulsivity and BRI are latent variables and thus latent endophenotypes) between input and output arrays as well as application of machine learning reinforcement learning in ANN applications (Delashmit & Manry, 2005; Durstewitz et al., 2019; Fan et al., 2023; Levin & Narendra, 1993; Subramanian et al., 2022). Similarly, neurocomputational models may employ genetic algorithms (applied to everything from EEG to schizophrenia and often used with machine learning support vector machines [SVM]), which roughly map as computational mimetics of evolutionary theory and natural selection at the gene (and allele) level, informed by binary probability theory (Anastasio, 2010; Bartlett et al., 2023; Chen et al., 2024; Goldberg, 1989; Mitchell, 1998; Langdon & Poli, 2010; Rashid et al., 2023; Saibene et al., 2023; Steeb, 2015).

The mathematics used in neurocomputational modeling includes calculus, including various forms of differential equations (ordinary, partial, stochastic); linear algebra, matrix algebra, graph theory, topology, discrete mathematics, symbolic and fuzzy logic, multivariate statistics, and Bayesian statistics (Anastasio, 2010; Anderson, 2014; De Schutter, 2010; Farahani et al., 2019; Mallot, 2013; Petzschnner et al., 2017; Riaz & Jamil, 2023; Sanchez, 2021). They

often involve linear approximations of non-linear systems or numerical (approximate fitted model) solutions rather than analytical (precise) solutions (Anastasio, 2010; Anderson, 2014; De Schutter, 2010; Mallot, 2013; Sanchez, 2021). Neurocomputational programming (modeling) environments include open-source programming languages Python, R, and Julia, and proprietary programming environments like Matlab, NetLogo, and STELLA (Anastasio, 2010; Richmond, 2004; Wallisch et al., 2014; Yamada-Bagg, 2022; Yegenoglu et al., 2022). Discussion of these programming environments is beyond the scope of this review.

As noted above, real data is used to either train or otherwise provide inputs into neurocomputational models. Consequently, real world laboratory empirical studies, such as this study, are required to provide those inputs (empirical and mathematical preprocessing features). Empirical studies, such as this study, are often predicates to neurocomputational models to fit data theoretically, understand system mechanics, or predict (via continuous extrapolation or interpolation) system behavior. Further, since neurocomputational models attempt to approximate and understand the function and mechanisms of neural network systems inputs (and behavioral systems as operationalized embodiments of neural network systems), those inputs are often dimensionalized (decomposed) rather than dimensionally reduced as is common in empirical studies and AI (e.g., employing factor analytic methods such as exploratory factor analysis [EFA], confirmatory factor analysis [CFA], and principal component analysis [PCA]). Once the neurocomputational model processes decomposed inputs, machine learning and deep learning algorithms often employ similar factor analytic methods and other data transformation and processing algorithms to reduce the dimensionality of data so as to provide simpler representations of complex dynamical systems or to eliminate components or factors (called features in machine learning) whose elimination (via or as a consequence of feature

extraction) does not materially reduce the accuracy or precision of the neurocomputational model (Anderson, 2014; Mallot, 2013). This process thus reduces the computational resources required to run a model (Anderson, 2014; Mallot, 2013).

High dimensional data can typically exhaust computing resources. High dimensional data is data where there are more features than observations (Buhlmann, et al, 2014). For example, if a patient with ADHD, ASD, schizophrenia, or BPD, or groups of all those behavioral phenotypes, are genotyped for all candidate genes (alleles) implicated in those polygenic disorders, which can number in the hundreds or thousands or more, the result is more features (the alleles) than observations (presence of each allele in one patient). Similarly, a data set of all the sub-scales (features) of a self-report (e.g., BIS-11) or behavioral measure (e.g., SST) in a study of n subjects, outnumber the number of subjects. That is high dimensional data. Numerically, for example, for a sample of 1,000 subjects and 41 features (a 1,000 X 41 matrix), the BIS-11 provides 41,000 summary data points (13,000 scale/subscale measures), the GNG 15,000 (a 1,000 x 15 matrix) scale/subscale measures, SST 18,000 (a 1,000 x 18 matrix) scale/subscale measures, and WCST 37,000 (a 1,000 x 37 matrix) scale/subscale measures, for a total of 111,000 data points or 111 features per subject. Using only the 3 subscales used for each measure of this study, there are 1,800 measures per instrument for 7,200 total, or just 12 features per subject. By reporting only the top scale (or one sub-scale) of a self-report or behavioral measure, the dimensionality of the data is reduced even further to low dimensional data and is easier to process, computationally, mathematically, and statistically. However, in order to build a neurocomputational model, each subscale may need to be reported (feature selection) into the model to enable robust feature extraction and engineering (Erguzel et al., 2015).

Computational Psychology and Computational Psychiatry.

Arguably, the application of computational neuroscience to the operational embodiments of neural circuits and neural network systems in the form of cognition and behavior encompasses the subfield of computational psychology (Bartlett et al., 2023; Gheibi et al., 2023; Sun, 2008). The application of computational neuroscience, including computational and behavioral neuroscience, to DSM mental disorders (psychopathology) can be defined as computational psychiatry (Anticevic & Murray, 2018; Brucar et al., 2023; Fineberg et al., 2017; Friston, 2023; Iglesias et al., 2017; Karvelis et al., 2023; Khaleghi et al., 2022; Montague et al., 2012; Pauli & Lockwood, 2023; Petzschner et al., 2017; Redish & Gordon, 2016; Series, 2020; Stephan & Mathys, 2014; Wang & Krystal, 2014). Computational psychiatry is also a program explicitly created by the NIMH as a means of applying the RDoC's dimensional domains and units of analysis to behavioral phenotypes (psychiatric disorders; NIMH, n. d., 2023; Pauli & Lockwood, 2023). NIMH director Dr. Gordon coauthored a text on computational psychiatry and stated, in an interview with the journal *Science*, that neural circuits and computational psychiatry were his top priorities for the NIMH (Redish & Gordon, 2016; Gordon, 2016). Importantly, in that same interview, when explicitly disagreeing with the false notion that the RDoC is intended to replace the DSM, Dr. Gordon reflected a line of logic between the RDoC and the DSM suggested previously in this chapter and with respect to this study—that is, combining assessments using the RDoC and the DSM, mathematically, gives you more information (Gordon, 2016). That combination is essentially the field of computational psychiatry.

Neurocomputational models (digital twins) of behavioral phenotypes (psychiatric disorders) are models of entire neural and behavioral systems across RDoC's domains and units of analysis (Friston, 2023; Iglesias et al., 2017; Wang & Krystal, 2014). Such models are built on

the backs of developments in behavioral and psychiatric genetics that have identified candidate genes and GWAS arrays, neurophysiological and neuroimaging methods and studies (e.g., fMRI and qEEG/ERP/LORETA) that have identified functional loci and dopaminergic neural networks implicated in behavior (and cognition), including abnormal behavior; neuropsychological and psychometric methods and studies (RDoC paradigms; e.g., self-report and laboratory behavioral measures) that characterize and quantify that behavior, and clinical observations of symptoms that comprise psychological constructs, such as impulsivity (Duck et al, 2023; Erguzel et al., 2015; Friston, 2023; Hupen et al., 2023; Iglesias et al., 2017; Wang & Krystal, 2014).

Such neurocomputational models thus explicitly implicate the RDoC's underlying premise and goals, incorporating NDST principals, by first modeling DSM agnostic systems and behavior, and then developing specific models or digital twins of behavioral phenotypes, a key goal of this study (Iglesias et al., 2017; Montague et al., 2012). One cycle of study progression can be to first conduct empirical studies of specific aspects (model inputs or empirical and mathematical preprocessing features) of a behavioral system (e.g., decomposed endophenotypes of BRI, as in this study), use those inputs to develop a neurocomputational model of the system, fit the model to real world data using AI, including machine learning, multilayered artificial neural networks, and genetic algorithms; form a hypothesis informed by the model, test the hypothesis in empirical studies, feed results into an iterated model (including via use of AI enabled reinforcement learning), and then apply or implement the model into translational research of behavioral phenotypes, and finally, build a model or digital twin of a behavioral phenotype (Abilkaiyrkyzy et al., 2024; Chen et al., 2024; Fan et al., 2023; Friston, 2023; Iglesias et al., 2017; Montague et al., 2012; Saibene & Gaspaini, 2023; Spitzer et al., 2023; Subramanian et al., 2021; Wang & Krystal, 2014). Examples of this progression follow next, first with

neurocomputational models of impulsivity and BRI, next via discussion of neurocomputational clustering of the DSM nosology, next with a high level survey of applications of AI (machine learning and deep learning) to research of each behavioral phenotype that is the focus of this study, namely ADHD, ASD, schizophrenia, and BPD; and then with examples of one study focused on a theory driven mechanistic neurocomputational model and one study focused on an atheoretical data driven clustering model for each of those behavioral phenotypes.

Neurocomputational Models of Impulsivity and BRI. As previously discussed, endophenotypes related to impulsivity (and compulsivity) merge at deficits in behavioral response inhibition (BRI). Such endophenotypes range from genetic markers (candidate genes or GWAS alleles), to quantitative trait loci (QTL), to neurobiological endophenotypes comprising dopaminergic neural network components or elements (from qEEG/ERP, for example), to neuroanatomical functional loci (from fMRI, for example), to neuropsychological endophenotypes (from self-report and laboratory behavioral measures) across the RDoC units of analysis continuum (Iglesias et al., 2017; Wang & Krystal, 2014). Across that DSM agnostic continuum of endophenotypes, patterns emerge or latent phenotypic clusters are discovered that are often best teased out using neurocomputational models that map to specific behavioral phenotypes (Iglesias et al., 2017; Wang & Krystal, 2014). The better the inputs (empirical and mathematical preprocessing features) fed into the model (high quality decomposed [deep] endophenotypes), the more accurate a differential neurocomputational model (digital twin) of a behavioral phenotype (e.g., ADHD, ASD, schizophrenia, BPD) can be developed (Anticevic & Murray, 2018; Iglesias et al., 2017; Redish & Gordon, 2016; Series, 2020; Wang & Krystal, 2014)). The dynamic training of the model (extrinsically, or intrinsically via Bayesian adaptation for example) and dimensional reductions needed can be accomplished using the tools of AI,

statistical machine learning, and deep learning (multilayered artificial neural networks), or genetic algorithms, including use of NDST mathematics (Anticevic & Murray, 2018; Chen et al., 2024; Montague et al., 2012; Redish & Gordon, 2016; Saibene & Gasparini, 2023; Series, 2020; Wang & Krystal, 2014).

Fundamental to neurocomputational model development is the identification (selection), reduction (extraction), and assembly (engineering) of features that have the highest predictive and differential loading and best contribute to phenotypic differentiation or discrimination (Guyon & Elisseff, 2003; Guyon & Elisseff, 2006; Hastie et al., 2009; James et al., 2021; Janssen et al., 2018; Tai et al., 2019). A feature is a term used in machine learning to represent independent, dependent, intermediate, and floating variables used to build or train machine learning models (Built In., 2024; Guyon & Elisseff, 2003; Hastie et al., 2009; James et al., 2021; Janssen et al., 2018). Feature selection is the process of selecting a subset of variables that most strongly and efficiently (computationally) contribute to building a good predictor for machine learning (Guyon & Elisseff, 2003; Hastie et al., 2009; James et al., 2021). Feature selection approaches include wrapper methods (scoring of feature subsets via learning), embedded methods (feature selection during training), and filter methods (preprocessing approaches; Guyon & Elisseff, 2003; James et al., 2021). As described in Chapter 3 and 4, the present study used a theoretic filter based preprocessing feature selection method (i.e., MANOVA followed by post hoc tests using p -value statistical criterion scoring independent of any statistical machine learning model) as a multi-class problem (multivariate) structured as a two-class machine learning classifier (Guyon & Elisseff, 2003; James et al., 2021). Feature engineering focuses on the selection (including from feature selection methods), manipulation, and mathematical transformation of variables (raw data) into, and extraction of, features that can be optimally and

efficiently incorporated into machine learning models (Built In., 2024; Hastie et al., 2009). It consists of five processes: feature creation or selection, variable or feature mathematical transformation, feature extraction, variable or feature exploratory data analysis, and benchmarking (Built In., 2024). As described in Chapter 3 and 4, the present study used Cook's leverage-residual (influence) sensitivity analysis and Cross-Model Convergent Analysis to manipulate, transform, extract, and robustly explore data variables to engineer selected features into a framework of new feature spaces (frameworks) comprising linear variates as higher powered predictors for machine learning (Built In., 2024).

Feature extraction (independent of or after feature selection and as part of feature engineering) involves derivation or extraction of features (via dimensional reduction or mathematical transforms) that most contribute to variation in a system, including features that can be extracted from targets (dependent variables), comprising noise, that features fail to predict (Bishop, 2006; Guyon & Elisseeff, 2006; Hastie et al., 2009; Janssen et al., 2018). Machine learning algorithms are pattern recognition algorithms (classifiers) and overfitting of a model due to failure of a feature to predict an outcome measure results in what is called a false optimal classifier (of a fitted data set; Janssen et al., 2018). The RDoC, after all, is a "feature-condition correlation matrix" (Tai et al., 2019, p. 3). Extracting features with the strongest predictive capability can often be accomplished via feature inputs (empirical and mathematical preprocessing feature selection) derived from studies, such as this study, and then refined (feature extraction) in models of larger systems via exploratory factor analysis (EFA; using support vector clustering [SVC], for example) or principal component factor analysis (PCA) enabled unsupervised machine learning algorithms (Tai et al., 2019). The subscales of the BIS-11, GNG, SST, and WCST that are the focus of this study are examples of putative selected

features as endophenotypes that can be extracted and engineered into frameworks of features as deep endophenotypes that can help discriminate deficiencies in BRI across behavioral phenotypes.

Speaking to the issue of better model inputs (features), with respect to endophenotypes of impulsivity and BRI, Wang and Krystal (2014), for example, have noted a need to fill the very gap this study was intended to fill. They noted that “there remains a hope that endophenotypes may be more precisely defined, measured, and related to the underlying biology” (Wang & Krystal, 2014, p. 643). Wang and Krystal (2014) observed that the historical unitary treatment of impulsivity and BRI (noting their transdiagnostic nature) is flawed and that each may be decomposed into processes (facets, components, factors, features) that can each serve as candidate endophenotypes. Wang and Krystal (2014) then posited that improved endophenotypes of impulsivity and BRI can then be used to develop theories from neurocomputational models as applied to both neurotypical and clinical populations and iterate model development to map onto specific behavioral phenotypes including ADHD, ASD, schizophrenia, and BPD, from models of DSM agnostic RDoC dimensionally framed psychological constructs of impulsivity and BRI.

In the end, one application of neurocomputational models of DSM behavioral phenotypes is to provide so called computational assays that can be mapped onto neuropsychological (behavioral) and neurobiological (neuroimaging, genetic etc.) data obtained from clinical and neurotypical populations and individuals, so as to inform differential diagnosis (Iglesias et al., 2017; Pauli & Lockwood, 2023; Stephan et al., 2015; Stephan & Mathys, 2014).

Neurocomputational modeling of DSM behavioral phenotypes has been explicitly implicated in the use of artificial intelligence (AI) machine learning (ML) tools to create psychiatric disease models (digital twins) to directly inform differential diagnosis and the development of

personalized behavioral and psychopharmacological interventions (treatments) for what are really multifactorial dimensional states and phases of psychiatric diseases (Tai et al., 2019). For example, applying that concept to BPD, a BPD neurocomputational model (digital twin) may assist in identifying the most optimal treatment modality described above in the BPD treatment section (e.g., DBT, transference-based therapy, mentalization based therapy, general psychiatric management or a combination of them) for a patient fitted to a model defining a unique BPD state and phase space (see Finberg et al. [2014] discussion below in the BPD section on neurocomputational models of behavioral phenotypes). In other words, a unique BPD behavioral phenotype with a unique mix of both risk factors (i.e., endophenotypes comprising candidate genes, neurobiological neuroimaging measures [e.g., P3/N2 waveform signature or fMRI footprint], and neuropsychological measures [e.g., subscales of BIS-11, GNG, SST, WCST]) plus unique symptomatic signatures from the DSM BPD criterion set. This is similar to personalized medicine in oncology where treatment modalities are often based on individual patients presenting with certain allelic polymorphisms known to increase disease liability for a subtype of the cancer and biological, physiological, and environmental risk factors.

Similarly, use of neurocomputational models that invoke machine learning algorithms to statistically process high dimensional multimodal neuroimaging data (i.e., arrays of multiple fMRI and qEEG/ERP feature sets per observation), such as support vector machines (SVMs, a supervised form of exploratory analytical processing algorithms) can be used prognostically (Duck et al, 2023; Erguzel et al., 2015; Hupen et al, 2023; Janssen et al., 2018; Stephan & Mathys, 2014). So, for example, a patient's fMRI image data and qEEG/ERP component and waveform complex data can be fed into neurocomputational multimodal-model of a statistical sample of neuroimaging data of BPD patients to predict general prognosis and treatment

outcomes. This process then informs further identification of psychiatric biomarkers and endophenotypes (Janssen et al., 2018). These endophenotypes can include neuroimaging data. Dynamic causal models (DCMs), discussed in the NDST section of this chapter, are an example of RDoC scaled nonlinear (generative) neurocomputational models applied to neuroimaging data (Stephan et al., 2015; Stephan et al., 2008; Stephan & Mathys, 2014). Other neurocomputational models have been developed for neuroimaging data of impulsive behavior and deficits in BRI.

Faouze et al. (2022) used a neurocomputational model implemented in Python that employed a type of artificial neural network (ANN; a deep [layered] learning form of AI) called a recurrent neural network (RNN) in addition to logistic regression algorithms, to study impulse control disorders in Parkinson's disease. RNN's are used to study complex NDST framed dynamic feedback systems (dynamic behavior; Dupond, 2019). The Faouze et al. (2022) model comprised a high dimensional feature space that included 50 candidate alleles, including dopaminergic alleles, and a plurality of Parkinson's implicated biomarkers (e.g., REM sleep patterns) and endophenotypes measured sequentially, and longitudinal pharmacological interventions (levodopa and dopamine agonists etc.). The goal of the neurocomputational model of Fouze et al. (2022) was to unbiasedly predict impulse control disorders in Parkinson's disease clinical samples.

Zhong et al. (2022) developed a neurocomputational model of BRI in Parkinson's patients that included all three facets under Barkley's theory discussed previously in this chapter, namely, prepotent response inhibition, prepotent response extinction, and interference control. The purpose of the model was to understand the mechanisms of, and to predict motor behavior in, neurotypical subjects versus Parkinson's patients (Zhong et al. 2022). Zhong et al. (2022) noted that most empirical studies do not study motor functions together, which makes it

challenging to formulate integrated mechanistic theories and hypothesis of action regulation (i.e., BRI). Their theory driven neurocomputational model employed two NDST theories, dynamic neural field (DNF) theory and stochastic optimal control theory (Zhong et al., 2022). Zhong et al. (2022) used data from a go/no-go (GNG) type task (for prepotent response inhibition), the stop-signal task (SST, for prepotent response extinction) and the flanker task (for interference control) to populate the model with neuropsychological inputs. However, Zhong et al. (2022) used top level reaction time (RT) behavioral scales and did not include additional decomposed scales implicated in BRI or subscales of self-report trait measures (such as the BIS-11) that relate to motor impulsivity, such as those used in this study. Their large scale high dimensional model was also loaded with neurobiological correlates including neuroimaging data (Zhong et al., 2022). Zhong et al. (2022) did not computationally operationalize their neurocomputational model, which presents the next step, by fitting to real world human neurobehavioral data, but contemplated use of genetic algorithms to accomplish systems level fitting.

Neurocomputational models have also been developed to understand the dopaminergic systems involved in impulsivity and BRI as well as neurological and behavioral phenotypes they implicate, including Parkinson's disease, ADHD, and schizophrenia (Duck et al., 2023; Hupen et al., 2023; Maia & Frank, 2011). Maia and Frank (2011), for example, invoked the RDoC and described the use of theory driven reinforcement learning neurocomputational models to model the dopaminergic cortico-basal ganglia-thalamo-cortical (CBGTC) loops, including the go mesolimbic direct (pleasure) neural pathway and the no-go mesocortical neural pathway, which can be differentiated by the GNG test. The model focused on D1 and D2 receptor dynamics extracted from electrophysiological (using EEG/ERP) data and network transition through functional loci including the dlPFC, OFC, and ACC, creating a BG-GNG (basal ganglia go/no-

go) model (Maia & Frank, 2011). Maia and Frank (2011) then implemented neurocomputational simulations of the BG-GNG model to Parkinson's disease, Tourette's syndrome, ADHD, drug addiction, and schizophrenia. Next follows a discussion of the literature regarding clustering (classifying) of behavioral phenotypes using neurocomputational approaches followed discussions of applications of AI (machine learning and deep learning) and development of neurocomputational models in the literature of the four behavioral phenotypes discussed in this chapter, ADHD, ASD, schizophrenia, and BPD.

Neurocomputational Clustering of Behavioral Phenotypes. The DSM nosology essentially comprises diagnostic categories defined by clusters of symptoms that were identified, segregated, and categorized from the top down by a panel of mostly clinical experts (Decker, 2013). Being pattern recognition engines in large part, neurocomputational models employing machine learning and deep learning (multilayered artificial neural networks) are very effective at interrogating high dimensional data for hidden clusters (hidden or latent structures) across scales, measures, and symptomatic observations. Neurocomputational models can bridge the gap between DSM nomological categories of heterogeneous symptoms that do not map onto their neurobiological substrates and underlying RDoC enabled domains and units of measure comprising endophenotypes that do. Consequently, neurocomputational models can both aid and supplement from the bottom up, the top-down nosology of the DSM.

Data driven atheoretical neurocomputational models can be used to stratify behavioral phenotypes including ADHD, ASD, schizophrenia, and BPD not only along symptom domains, but along entire RDoC scaling domains and units of analysis (Marquand et al., 2016b; Stephan & Mathys, 2014). Unsupervised machine learning algorithms, for example, are atheoretical data driven neurocomputational methods that are not fed classifiers (DSM diagnostic labels in this

case) to train the models but must extract hidden (latent) structures from the data to form groups or clusters (Marquand et al., 2016b; Tai et al., 2019). The two most common unsupervised machine learning segregation methods used in computational psychiatry are clustering and finite mixture models (Marquand et al., 2016b).

All clustering methods seek to segregate patients into clustered groups that share the most covariates in the data relative to other clusters (Marquand et al., 2016b). Common clustering methods include k-means clustering, but in computational psychiatry, hierarchical clustering and agglomerative clustering are particularly applicable to stratify behavioral phenotypes (Marquand et al., 2016b). Finite mixture models (FMMs) can also be used. FMMs all use finite probability distributions of components, including Gaussian mixture models (GMMs) and other probability distribution-based models, such as latent class cluster analysis (LCCA) that can process different types of data and intervariable dependencies (Marquand et al., 2016b; Stephan & Mathys, 2014).

The above clustering and FMM approaches appear to work well with neuropsychological endophenotype paradigms of the RDoC in combination with DSM syndromal and symptomatic criterion categories, but less so with gene level and other lower RDoC levels of analysis due to the problem of high dimensionality of polygenic data (Marquand et al., 2016b). To better incorporate higher dimension genetic and other neurobiological data, either AI dimensional reduction methods must be layered or deep learning methods implemented or normative models can be used based on deviations from normative behavioral ranges (Marquand et al., 2016a). Following is a discussion of the use of AI, including machine learning and deep learning in ADHD, ASD, schizophrenia, and BPD research, followed by examples of theory driven mechanistic neurocomputational models and data driven atheoretical clustering models for each of those behavioral phenotypes.

Artificial Intelligence, Machine Learning, and Deep Learning in ADHD research.

Neurocomputational methods invoking the tools of artificial intelligence (AI) statistical machine learning (ML) and deep learning (DL) are being used in behavioral phenotype research with greater frequency and scope. As discussed in more detail elsewhere in this chapter, many AI/ML/DL architectures are essentially pattern recognition engines (supervised using training classifiers or unsupervised to extract latent cross-correlated clusters of data) and, as such, can be utilized to classify behavioral phenotypes, such as ADHD, and thus further segregate (decompose) subgroups of patient populations to, for example, provide more precise targets for therapeutic intervention similar to precision (personalized) medicine in the field of oncology.

For example, Wang et al. (2023) used fMRI data (the classifier class) to develop two types of classifier deep learning (DL) models for ADHD. One model used convolutional neural networks (CNN) in combination with independent component analysis (ICA, a dimensional reduction technique), and the second used autoencoders (AE; autoencoders are multilayered neural networks that reduce the dimension [encode] of inputs into latent mimetics of those inputs and then decode those mimetics into outputs) to identify latent feature sets (Wang et al., 2023). Saurabh and Gupta (2024) developed a deep learning model for ADHD for resting-state fMRI (rs-fMRI) data using a bidirectional long short-term memory (BiLSTM) recurrent neural network (RNN) that automates voxelwise classifiers. Rupni and Priya (2024) developed a machine learning model to diagnose ADHD sub-types using T1-MRI data using a fuzzy c-means clustering algorithm. Graph theory and complex network theory, using eigenvector centrality (eigenvectors are discussed in detail in Chapter 3), for example, have also been used with machine learning methods such as classification and regression trees (CART) to classify ADHD patient clusters using fMRI data classifiers (Saha & Sarkar, 2024).

EEG data has also been a target classifier class for ADHD using machine learning (ML), including K nearest neighbor (KNN) and extreme gradient boosting (XGB); and deep learning (DL), including multilayer perceptron neural networks (MLPNNs), convolutional neural networks (CNNs), and recurrent neural networks (RNNs), though CNNs are a form of non-explainable AI in that they are essentially black box models (Ahire et al., 2023). Chauhan & Choi (2023) developed a machine learning model to distinguish EEG data (the classifier class) for ADHD patients and controls using a plurality of classifiers. Model modalities included support vector machines (SVM), Naïve Bayes (uses Bayesian statistics to determine class label priors), decision trees (hierarchical classifiers), random forest (ensembles of decision trees), and linear discriminant analysis (LDA; which is a dimensional reduction technique) with Naïve Bayes yielding the best results (Chauhan & Choi, 2023).

Neurocomputational Models of ADHD. As an example of a mechanistic neurocomputational model of ADHD, Veronneau-Veilleux et al. (2022) developed a mechanistic neurocomputational model of dopaminergic dynamics in ADHD. Veronneau-Veilleux et al. sought to virtually test whether ADHD dysfunction is related to phasic/tonic dopaminergic imbalance with a focus on D2 and D3 dopamine receptors and dopamine transporter (DAT; Veronneau-Veilleux et al., 2022). First, Veronneau-Veilleux et al. developed a model of tonic phase transitions of a dopaminergic system, including derivative phase transitions in collateral cortico-striatal systems during reinforcement learning processes (Veronneau-Veilleux et al., 2022). Their reinforcement learning model was previously used by the authors to study dopaminergic dynamics in Parkinson's disease (Veronneau-Veilleux et al., 2022). As discussed previously and in the method section of this Chapter, Reinforcement learning is a focus of the NDST enabled Dynamic Development Theory. Next, Veronneau-Veilleux et al. developed a

dynamic model of the basal ganglia and combined the two models to create an ensemble (Veronneau-Veilleux et al., 2022). Veronneau-Veilleux et al. iterated additional components of the model including virtual ADHD patients and controls to engage in a virtual reinforcement learning task (Veronneau-Veilleux et al., 2022).

As an example of a clustering neurocomputational model to map RDoC's dimensional endophenotype models to DSM categorical nosology, van Hulst et al. (2015) used latent class analysis (LCA) to stratify ADHD into clusters of neuropsychological measures rather than DSM criterion classifiers in 121 ADHD patients. The neuropsychological measures included a go/no-go (GNG) task to measure the RDoC cognitive control domain, explicitly implicating Barkley's theory of inhibitory deficits, which comprises BRI (Barkley, 1997a; van Hulst et al., 2015). The authors also assumed the dopamine transfer deficit theory (mentioned previously in the discussion of alternative theories considered for this study; van Hulst et al., 2015).

Pathophysiologically, the authors implicated fronto-striatal and ventro-striatal hypoactivation. The authors identified a strong poor cognitive control (deficient BRI) cluster of ADHD patients, the largest dysfunctional cluster of five clusters they identified. van Hulst et al. (2015) explicitly indicated that the model's identification of this strong cluster (BRI/cognitive control) mapped onto Barkley's theory. As discussed previously in the section on neurocomputational models generally, data driven (ML and DL) models can be applied in the context of a theoretical framework (i.e., Barkley's theory and the dopamine deficit transfer theory in the van Hulst et al. [2015] study). van Hulst et al. (2015) explicitly noted this is an example of this approach to parse heterogeneous groups of ADHD patients into homogenous neuropsychological clusters. The authors indicated such clustering represented an operationalization of the neurobiologically focused endophenotype hypothesis of the RDoC. van Hulst et al. (2015) did not, however,

discriminate facets of BRI under Barkley's theory or ascribe the GNG to a facet rather than BRI (cognitive control) overall. This represents a gap in neurocomputational model studies that can be informed by this study to provide more discriminating features for model design. In fact, in discussing the limitations of their study, van Hulst et al. (2015) noted that future studies would benefit from better discriminated task measures.

Artificial Intelligence, Machine Learning, and Deep Learning in ASD research.

Common among the four behavioral phenotypes discussed in this study is the multifactorial symptomatic heterogeneity and multimodal means of measurement for the purpose of diagnosis, prognostic evaluation, and treatment. These can involve non-linear and plural covariates.

Artificial intelligence (AI), including machine learning (ML) and deep learning (DL) can inform these complexities. In ASD research, AI related methods have become increasingly critical in this regard as evidenced by numerous systematic reviews.

For example, Jia et al. (2024) systematically evaluated early diagnostic markers of ASD (e.g., gaze behaviors, facial expressions, motor movements, task measures) by reviewing studies that used machine learning and deep learning, including convolutional neural networks (CNN), K-nearest neighbor (KNN), long-short term memory (LSTM) recurrent neural network (RNN), support vector machines (SVM), random forest (RF), deep neural networks (DNN), Naive Bayes, and non-ensemble decision trees. Das et al., (2023) conducted a systematic review of machine learning studies using primarily SVM machine learning and K-nearest neighbor and deep learning using convolutional neural networks (CNNs), with EEG and MEG data for ASD diagnosis. Li et al. (2024) built on prior reviews and conducted a systematic review of the use of AI for the diagnosis of ASD using EEG data (including unimodal and multimodal ASD comparisons). The authors evaluated the use of machine learning including support vector

machines (SVM, including use of NDST enabled kernels [which permit linear classifiers to solve nonlinear problems], K nearest neighbor (KNN, including use of Lyapunov exponents from NDST), ensemble random forest (RF), and logistic regression (LR, a binary classifier); and deep learning methods including and multi-layer perceptron neural networks (MLPNN), recurrent neural networks (RNN) including long-short term memory (LSTM and BiLSTM) variants, convolutional neural networks (CNN), autoencoders (AE), and graph convolutional networks (GCN; Li et al., 2024). Li et al. (2024) provided a detailed description of the pre-processing (down-sampling, re-referencing, normalization, artifact removal), processing (feature extraction), and classification of EEG data from ASD samples (time domain features, frequency domain features, time-frequency domain features [using fast Fourier transforms]) via machine learning.

Neurocomputational Models of ASD. As an example of a neurocomputational model of ASD (and OCD) decision dynamics, Carlisi et al. (2017) developed a mechanistic neurocomputational model of underlying neural correlates in 24 boys with ASD, 20 with OCD, and 20 controls in the context of reinforcement learning. The model identified shared dysfunction for ASD and OCD in the lateral-(orbito)fronto-striatal reward circuitry (Carlisi et al., 2017). However, only the ASD group had hyperactivation of the lateral inferior frontal/insular system (Carlisi et al., 2017). The premise of the model is the overlapping preservative and compulsive behaviors of the two disorders due to shared genetic liability and neurobiological correlates (Carlisi et al., 2017). As discussed previously in this chapter, the impulsivity of ASD and compulsivity of OCD merge at deficits of BRI. The authors used the Iowa Gambling Task (IGT; discussed previously) as the neuropsychological measure. fMRI was used for functional neuroimaging while subjects undertook the IGT (Carlisi et al., 2017). IGT task measures and fMRI measures comprised RDoC model inputs in addition to DSM symptomatic criterion data,

among other categorical and biomarker metrics (Carlisi et al., 2017). The neurocomputational model used hierarchal Bayesian analysis (HBA) in the R programming environment (Carlisi et al., 2017). IGT data was fitted into the model using three theoretical models for the IGT and each was inferred using a mathematical statistical sampling method called Markov Chain Monte Carlo (MCMC; Carlisi et al., 2017), which is based on stochastic NDST dynamical inferences, in this case, using Bayesian probability distributions. In discussing the limitations of their study and ideas for future studies, Carlisi et al. (2017) suggested use of neuropsychological measures that better discriminate DSM behavioral phenotypes in the context of transdiagnostic (RDoC) correlates. Considering the overlap between ASD and OCD at deficits in BRI and its underlying neural circuit systems as discussed by Carlisi et al. (2017) and elsewhere in this chapter, the authors are essentially suggesting better discrimination of BRI and its measures and associated neurobiological measures, similar to the goal of this study.

As an example of the value of neurocomputational clustering models to help homogenize polygenic phenotypically heterogeneous DSM disorders like ASD, Fountain et al. (2012) developed a clustering neurocomputational model of developmental trajectories of ASD. The goal of the model was to map RDoC neurobiological correlates onto dynamic longitudinal symptomatic criterion measures in almost 7,000 children with ASD in a high dimension data set and extract homogenous clusters in the data with similar developmental trajectories (Fountain et al., 2012). The model employed a latent variable extraction method (latent class growth analysis [LCGA]) to identify trajectories fitted by Bayesian information criterion (BIC; Fountain et al., 2012). The model identified six developmental trajectories categorically ranging from low functioning to high functioning and including a feature extracted ‘bloomers’ category of patients

who started as low functioning but developed into high functioning patients (Fountain et al., 2012).

Artificial Intelligence, Machine Learning, and Deep Learning in Schizophrenia

Research. As with the other three behavioral phenotypes of this study, schizophrenia is polygenic, multifactorial, and multimodal, difficult to properly diagnose (particularly early) and characterize and successfully treat (as previously discussed, the earlier the diagnosis, the earlier the treatment, the better prognosis). Consequently, schizophrenia can benefit from the use of AI tools for diagnosis and characterization, particularly when EEG is one of the multimodal units of measure used. Whether the best AI tool for schizophrenia classification, characterization, and diagnosis using EEG data (or other types of neuroimaging data) is a machine learning tool or a deep learning tool depends on several factors. If features are well defined (i.e., suitable for supervised learning), data sets of relatively lower complexity and dimension, computational resources relatively limited, or use in a clinical setting require transparency (i.e., an explainable AI solution, see Chapter 5), machine learning tools may be better suited (He et al., 2024; Li et al., 2020; Rahul et al. 2024). If the data set is complex and of much higher dimensionality and better suited for automatic feature selection, and computational resources ample and extensive, deep learning tools may be better suited (Li et al., 2020; Lujan et al., 2023; Rahul et al., 2024).

Verma et al. (2023) systematically reviewed various machine learning (support vector machines [SVM], decision trees [DT], ensemble random forest [RF], K nearest neighbor [KNN]) and deep learning (ANNs, convolutional neural networks [CNNs], feed forward neural networks, recurrent neural networks [RNNs], multilayer perceptron neural networks [MLPNN], long short term [LSTM] recurrent neural networks [RNNs], or discriminate autoencoders [DANs]) methods to interrogate structural MRI, DTI, fMRI, and EEG data for schizophrenia diagnostic

classification. Rahul et al. (2024) systematically reviewed machine learning (support vector machines [SVMs] and decision trees [DTs], including random forests [RF], K nearest neighbor [KNN], and logistic regression [LR]) and deep learning (convolutional neural networks [CNNs] and recurrent learning based long-short term memory networks [LSTMs] and other recurrent neural networks [RNNs]) methods for classifying schizophrenia using EEG data.

Deep learning, and convolutional neural networks (CNN) in particular, have proven very accurate classifiers (as a Euclidian space classifier of non-Euclidian spatially discontinuous discrete data) of EEG data (due to its spatio-temporal complexity) for schizophrenia. Xu et al. (2024) used a spatio-temporal residual graph (using graph theory) convolutional neural network (STRGCN; using EEG channels as nodes) to develop a deep learning model to identify electrophysiological markers for schizophrenia classification. This approach enabled both single EEG channel temporal causal feature extraction and cross-channel topological correlation feature extraction (Xu et al., 2024). Sunil et al. (2024) also used graph theory enabled DL methods to interrogate fMRI data for schizophrenia (fMRI data is also non-Euclidian). The authors developed a deep graph convolutional neural network (DGCNN) schizophrenia biomarker (if not endophenotypic) classifier (using morphological regions of interest [ROIs]) model (Sunil et al., 2024). DGCNN proved a superior classifier to GCNs as well as random forest (RF), adaptive boosting (AdaBoost), K-nearest neighbor (KNN), support vector machine (SVM), and logistic regression (LR, Sunil et al., 2024). Machine learning (via supervised SVMs with linear kernels) and deep learning (via MLPs) methods have also been developed to interrogate structural MRI data, which is two dimensional and not optimal for CNNs, with XAI (explainable AI) post classification (Jiminez-Mesa et al., 2023). Ellis et al. (2023) used a one-dimensional convolutional neural network (1D-CNN) followed by K-means clustering to diagnose

schizophrenia using rs-fMRI dynamic functional network connectivity (dFNC) data. Turk et al. (2024) used a residual neural network (ResNet, a very deep neural network well fitted to EEG pyramidal architectures) to diagnose schizophrenia from EEG wavelet data.

Neurocomputational Models of Schizophrenia. As an example of a hypothesis generating mechanistic neurocomputational model of schizophrenia, Waltz et al. (2011) developed a model to test the hypothesis of deficient reinforcement learning as evidenced by neuropsychological measures, such as the Wisconsin card sorting test (WCST) as a proxy for prefrontal cortical (PFC) dysfunction. The authors invoked theories, including the dopamine hypothesis of schizophrenia discussed previously in this chapter. These theories related to dopaminergic dysfunction of striato-cortical basal ganglia neural network circuits via D1 and D2 dopamine receptors in go/ (reward circuit) and no-go (inhibitory) neural projections (Waltz et al., 2011). Thus, the authors used a go/no-go (GNG) task to test the hypothesis in 37 schizophrenia patients and 23 controls (Waltz et al., 2011). But the GNG task in Waltz et al. (2011) employed reinforcement learning probabilistic reward to load prepotency to a go response. The neurocomputational model bifurcated the direct reward basal ganglia (substantia nigra pars compacta [SNc]) D1 driven go neural pathway and the indirect inhibitory D2 driven no-go neural pathway (Waltz et al., 2011). As with many neurocomputational models, the model in Waltz et al. (2011) computationally tracked the behavioral study. The Waltz et al. (2011) model confirmed and therefore properly fitted, empirical findings that schizophrenia patients have deficient direct go D1 enabled neural function.

As an example of a clustering neurocomputational model to test NDST enabled dynamical neuronal circuit mechanisms from fMRI data in schizophrenia, Brodersen et al. (2014) developed a dynamic causal model (DCM) model to identify clusters via generative

embedding (a type of mathematical dimensional reduction). Brodersen et al. (2014) first re-analyzed fMRI data for 41 schizophrenia patients and 42 controls while performing a neuropsychological behavioral task measure. The authors then identified a feature space for the model of PFC network using a DCM generator as inputs into both supervised and unsupervised machine learning paradigms (Brodersen et al., 2014). The authors first used support vector machine (SVM) machine learning algorithms to classify (generate clusters) and to predict diagnostic labels. Next the authors used an unsupervised Bayesian Gaussian mixture model (GMM) to further stratify patients into unique clusters that covary with unique prefrontal (PFC) network architecture (Brodersen et al., 2014). The authors noted that their model is exemplary of the benefits of using neurocomputational models to cluster schizophrenia patients into groups defined in terms of RDoC enabled neurophysiological mechanisms.

Artificial Intelligence, Machine Learning, and Deep Learning in BPD Research. As previously suggested, perhaps the most complex and challenging behavioral phenotype is BPD, largely due to its symptomatic heterogeneity (including multifactorial impulsivity), substantial comorbidity, state and phasic non-linear or apparently non-linear oscillatory transitions (invoking NDST), and resistance to treatment. Numerous studies have sought to classify BPD and identify separable patient clusters using multivariate statistical methods, including finite mixture models (FMMs; Lenzenweger et al., 2008; Oladottir et al., 2022; Smits et al., 2017). While AI (machine learning and deep learning) tools provide more sophisticated statistical tools, most useful is AI's ability to perform adaptive iterative and recursive automatic clustering (and thus auto-diagnosis via pattern recognition inference engines) to identify latent patient cluster classifiers and diagnostic (including differential diagnosis) and treatment targets. This is particularly the case when machine and deep learning Bayesian statistical engines are used to

interrogate data from putative neurobiological and neuropsychological biomarkers and endophenotypes. De la Fuente et al. (2011) developed a Bayesian networks machine learning model to interrogate multimodal neurobiological and neurophysiological data (EEG and endocrine systems data) to identify pathophysiological correlates (biomarkers or endophenotypes) of BPD. Lahnakoski et al. (2024) used machine learning support vector machines (SVMs) to identify BPD classifiers from fMRI data from 116 patients and 72 neurotypical controls. Nazari et al. (2024) used machine learning K-nearest neighbor (KNN, which is statistically non-parametric) after considering other methods (support vector machines [SVMs], random forest [RF], and neural networks) to differentially diagnose BPD and bipolar disorder (often difficult to distinguish in some patient clusters despite their treatments often contraindicated in each other) using multimodal data from EEG and the WCST and achieved a 93% accuracy. Jafari et al. (2023) used machine learning Logistic LASSO (Least Absolute Shrinkage and Selection Operator) Regression (LLR) to interrogate multimodal fMRI (a neurobiological measure) and task measure data (a neuropsychological measure) in BPD patients and controls. Yin et al. (2023) used machine learning LASSO regression to predict treatment response in a patient pool of 105 BPD patients for dialectical behavior therapy (DBT, described previously). Grecucci et al. (2023) used ensemble machine learning (unsupervised multimodal canonical correlation analysis with ICA [independent component analysis] and supervised random forest [RF]) to diagnose BPD from neural network circuit white and gray matter densities. One of the networks in BPD patients that the authors identified covaried with impulsivity as distinct from controls with alterations in white matter density in the inferior frontal gyrus (IFG) and gray matter insula, which the authors noted are linked to BRI (Grecucci et al., 2023).

Neurocomputational Models of BPD. As an example of a neurocomputational model of reinforcement learning in BPD, Fineberg et al. (2014) developed a model of the inference engine in BPD patients used to perceive others. Their theory driven model assumes that BPD patients infer information about others from their own somatic experiences (Fineberg et al., 2014). Their model involved the classical application of computational neuroscience to psychopathology via computational psychiatry. The authors invoked theory driven models using Bayesian probability distributions to characterize statistically significant departures from normative mental functioning into mental disorder (Fineberg et al., 2014). The models then generate and test hypothesis regarding such departures and then use atheoretical data driven models to inform nosological clustering, diagnosis, and treatment (Fineberg et al., 2014). Consequently, Fineberg et al. (2014) noted that use of their neurocomputational model parameters may inform subsequent clustering models to inform personalized treatments (e.g., DBT or schema-based therapy discussed in the BPD section of this chapter) as suggested previously for BPD in the discussion of neurocomputational models of impulsivity and BRI. The model assumes BPD is characterized by prediction errors in inferential neuronal processing of environmental stimuli resulting in maladaptive associations that are compounded and become prepotent maladaptive responses to future categorically homogenous future stimuli (Fineberg et al., 2014). The prediction errors are derivative of aberrant object relations internal models of self (Fineberg et al., 2014). The authors posited that a computational psychiatry (RDoC) enabled neurocomputational model incorporating theoretical models with neuropsychological (behavioral) and neurobiological data can identify endophenotypes to aid in diagnosis or cluster more homogenous behavioral phenotypes of BPD and identify personalized treatment modalities (Fineberg, et al., 2014). Consistent with the transdiagnostic perspective of the RDoC, Fineberg et

al. (2014) noted that their model may be potentially applied to other DSM disorders characterized by perceptual difficulties in predictive inferential neural processing systems including ASD and schizophrenia, although neurocomputational models often identify substrates unique to a particular DSM category or sub-category. For an example of a predictive neurocomputational generative model that expands on the cognitive distortions from endogenous physiological states that lead to emotional dysregulation in BPD, see Seth (2013).

As an operationalized and productized example of a neurocomputational clustering model of BPD, Khazbak et al. (2021) developed a neurocomputational model that parameterizes inputs from real time events (behaviors, cognitions, environmental stimuli) from BPD patients that are then fitted to symptomatic categories to stratify BPD patients into homogenous clusters. The model uses differential machine learning classifiers to extract features to form differential BPD clusters (Khazbak et al., 2021). Machine learning classifiers included Naïve Bayes classifier, support vector machines (SVM), K-nearest neighbor (KNN), and long short-term memory (LSTM) recurrent neural network (RNN) models (Khazbak et al., 2021). The authors observed that SVM and LSTM best fitted clusters of BPD patients (Khazbak et al., 2021). For a comprehensive discussion of applications of computational psychiatry in BPD see Fineberg et al. (2017).

Summary

This chapter presented an overview of the state of the literature that frames the foundation and need for a quantitative quasi-experimental ex post facto study examining relationships between trait motor impulsivity on the BIS-11 and laboratory behavioral measures of behavioral response inhibition (BRI). This quantitative ex-post facto quasi-experimental study aimed to address a key problem in the literature: the endophenotype literature fails to adequately

characterize and segregate the dimensionality of the latent psychological constructs of impulsivity and impulse control (i.e., behavioral response inhibition [BRI]). This study sought to discriminate, segregate, and dimensionalize neurobiological and neuropsychological measures (endophenotypes) through assessing the relationships between subscales of the Barratt Impulsiveness Scale (BIS-11) for low and high trait motor impulsivity (the independent dichotomous predictor variable) and lower order subscales of each of three laboratory behavioral measures of BRI: the go/no-go task (GNG), stop signal task (SST), and the Wisconsin card sorting test (WCST; the dependent outcome variables). The outcome led to decomposed endophenotypes comprising deep endophenotypes that better discriminate behavioral phenotypes closer to their biological substrates as more precise inputs to latent variable neurocomputational models.

Theoretical Frameworks

Two theoretical frameworks framed this study. First, the Research Domain Criteria (RDoC) developed by the National Institutes of Mental Health (NIMH), founded on the endophenotype hypothesis and NDST principals; second, Barkley's theory of inhibitory deficits.

The Research Domain Criteria (RDoC), NDST, & Endophenotype Hypothesis. The Research Domain Criteria (RDoC) was promulgated by the National Institutes of Mental Health (NIMH, 2023). The DSM and ICD define psychopathology (and traits) based on symptomatic deviations from normalized behavior. The RDoC, in contrast, creates observable behavioral domains, constructs, and sub-constructs for psychopathological states, each firmly grounded in neurobiological and neuropsychological etiology and measures (units of analysis) and founded in behavioral neuroscience (Gagnon et al., 2022; Kozak & Cuthbert, 2016; NIMH, 2023; Sanislow et al., 2022). The RDoC attempts to reconcile an apparently false premise in the literature, that

categorical DSM mental disorders (behavioral phenotypes) are unitary constructs with unique pathophysiology and psychopathology that can be tied to specific unique neurobiological etiology (Kozak & Cuthbert, 2016).

NDST is a theoretical paradigm in mathematics that focuses on systems that have dynamical (subject to change) properties in that multiple variables within the system can change along a time series under different parametric phase transitions that are non-linear (i.e., they are stochastic [random] and non-deterministic) or are apparently, but not actually, non-linear (i.e., they are chaotically deterministic; Guastello & Gregson, 2011). Because most complex biological systems, such as the brain and its neural network systems (the focus of the RDoC), behave in a non-linear or apparently non-linear fashion, NDST is ideal for use in behavioral neuroscience (Jaeger & Monk, 2014; Sun & Wu, 2015). NDST focuses on feed-back loops between variables and accounts for temporal transitions between states, which can transition forward as well as backward, temporally or contingently (Gelfand & Engelhart, 2012).

An endophenotype is a latent non-obvious and non-apparent or otherwise hidden variable that comprises a mediational phenotype that can, nonetheless, be quantitatively measured by proxy and used in the etiological inquiry of the path from genotype to behavioral phenotype (Gottesman & Gould, 2003). The endophenotype hypothesis posits that lower order mediators, such as cognition and impulsivity (which can be both symptoms or endophenotypes), of downstream DSM behavioral phenotypes (mental disorders), may better map onto neurobiological correlates than onto the more complex DSM behavioral phenotypes, which are syndromal aggregates of symptoms (Gagnon et al., 2022; Kozak & Cuthbert, 2016). Consequently, endophenotypes facilitate determination of the functional consequences of given allelic genotypes— that is, the biological etiology of a cognate behavioral phenotype, which can

inform not only personality psychology, but also abnormal psychology and a DSM diagnostic regime and nosology that is phenomenological and not etiological (Chen et al., 2012; DiLalla et al., 2017; Ritsner & Gottesman, 2009; Robbins et al., 2012; Sanchez-Roige & Palmer, 2020; Walters & Owen, 2007).

The endophenotype hypothesis presumes certain criteria for putative endophenotypes in context of their decomposition (deep endophenotyping). First, endophenotypes can be, and perhaps should be, agnostic to psychopathology and thus transdiagnostic. In that sense, they are akin to pleiotropic genes, in that they influence putatively differentiated behavioral phenotypes. Trait motor impulsivity and, by antecedent association, BRI is, after all, pervasive in a plurality of psychopathologies and considered a strong candidate endophenotype (Crosbie et al., 2008; Robbins et al., 2012).

Second, the endophenotype hypothesis assumes lower order polygenic determinism than its manifest behavioral phenotype. That is to say, the endophenotype should, at a minimum, have fewer susceptibility genes or risk alleles than the behavioral phenotype. Further, as one continues to decompose an endophenotype (as this study did), one arguably should get closer to monogenic Mendelian etiology, since multifactorial polygenic disorders (behavioral phenotypes) like ADHD, ASD, schizophrenia, and BPD have a panoply of genotypic risk alleles. Each risk allele exerts a relatively small effect on the behavioral phenotype, owing to replicability and small effect size issues in the genome wide association, gene linkage, and candidate gene literature. Fewer risk alleles should each exert larger effects (Crosbie et al., 2008; Sanchez-Roige, 2020).

Third, following from the second point above, a given endophenotype, such as trait motor impulsivity, may not be a unitary construct, and include lower order facets, such as BRI, and, similarly, such lower order facets may not be unitary constructs, as suggested, in this case, by

Barkley's theory of inhibitory deficits. Consequently, it should differentially implicate a unique neurophysiological or neurobiological correlate, such as a unique EEG-ERP waveform signature, representing a unique neural network or unique network dynamics, as the case may be.

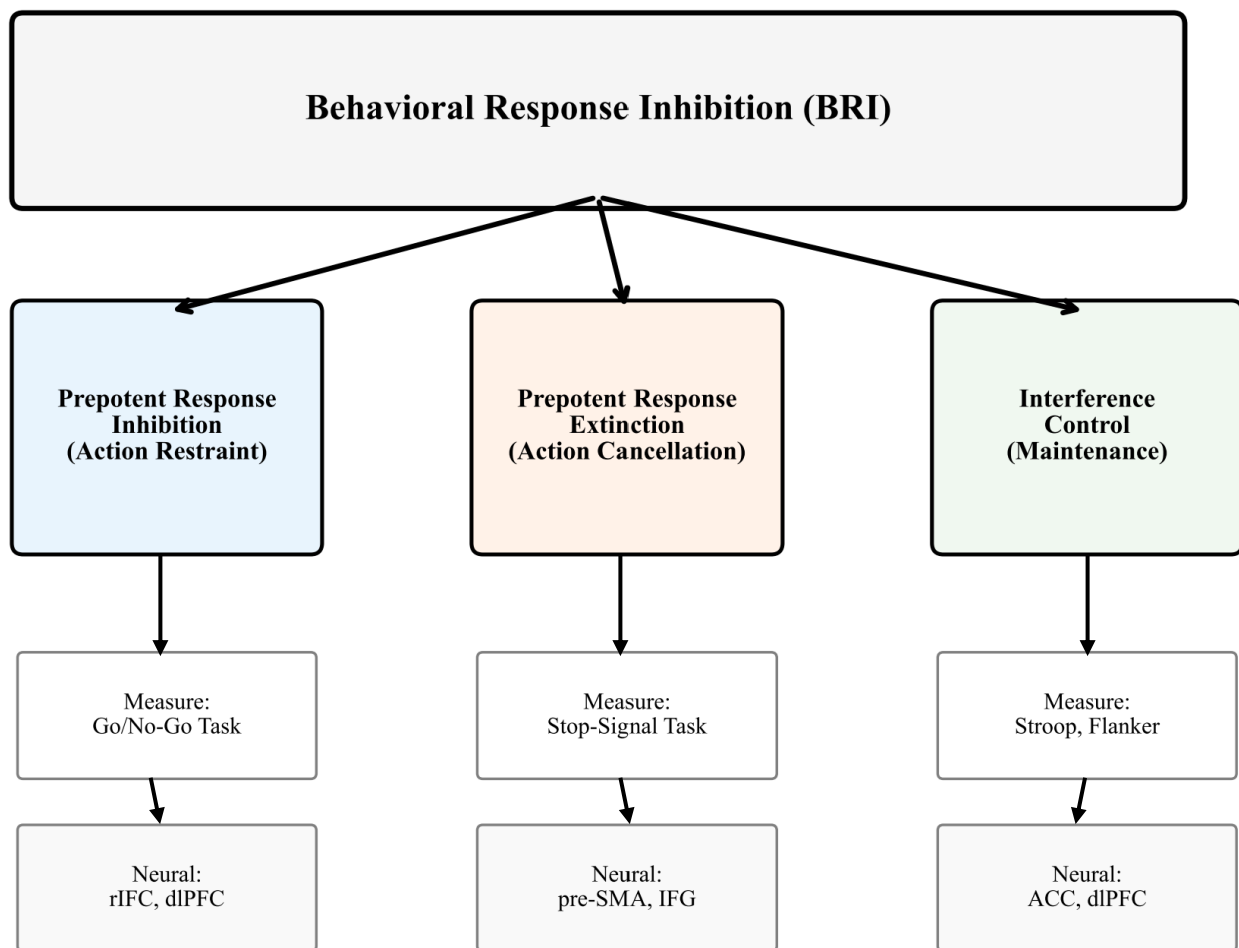
Fourth, in light of the above emergent features, —that is, the phylogenetically more primitive, and thus arguably developmentally earlier, position of a given endophenotype in relation to a behavioral phenotype, its agnostic or pleiotropic like relation to behavioral phenotype, and decomposition of endophenotype complexity to inform unique system behaviors— endophenotypes should serve as early predictors or primordial diagnostic markers, in healthy pre-symptomatic and prodromal individuals, of downstream behavioral phenotypes.

Barkley's Theory of Inhibitory Deficits. The second theoretical foundation of the probed study is Barkley's theory of inhibitory deficits. Barkley (1997a) posited that deficits in behavioral response inhibition (BRI), which implicate impairments in neurobiological prefrontal cortical functional systems including prefrontal, right inferior prefrontal, orbitofrontal, and striatal ventromedial neuroanatomical regions and their associated dopaminergic neural network systems, are seminal to ADHD (Barkley, 1997a; Crosbie et al., 2008). Barkley (1997a) posited that proper functioning of BRI is a condition precedent to proper functioning of four higher order neuropsychological cortical executive functions in that the inhibitory process creates the delay (a cognitive moment) necessary for these executive functions to be properly engaged. Barkley (1997a, 1997b, 1997c) parsed three facets or categorical processes of behavioral response inhibition: (a) prepotent response inhibition (action restraint or stopping before starting), which comprises inhibition of a response that is subject to the availability of immediate positive or negative reinforcement or for which such reinforcement has been primed through conditioning, (b) inhibition (prepotent response extinction) of an ongoing response (action cancellation or

stopping after starting) that has already begun, and (c) maintenance of the inhibitory process (interference control). Barkley's categorical distinctions suggest distinct processes and complex systems that have unique neurobiological and neuropsychological underpinnings including separate dynamical dopaminergic neural network systems, or at least separate system dynamics, to operationalize them. Figure 6 illustrates Barkley's three facet model along with its measures and neural correlates discussed later.

Figure 6

Barkley's Three-Facet Model of Behavioral Response Inhibition



Note: rIFC = right inferior frontal cortex, dlPFC = dorsolateral prefrontal cortex, pre-SMA = pre-supplementary motor area, IFG = inferior frontal gyrus, ACC = anterior cingulate cortex.

Scope of Literature Review

The literature review relevant to this study took into account the interdisciplinary approach of the RDoC and was appropriately multidimensional. First, behavioral and psychiatric genetics framed the endophenotype literature and the types of studies used to determine and quantify genetic liability. Second, the expansive endophenotype literature for both impulsivity and BRI as well as the four behavioral phenotypes of this study illustrated the scale agnostic continuum of putative endophenotypes along the RDoC's dimensional domains and units of analysis. Third, the impulsivity literature, including the literature on behavioral response inhibition (BRI) and their dimensions framed the RDoC informed transdiagnostic specific application of this study. Fourth, the bridge from the RDoC to the DSM focused on four DSM behavioral phenotypes that are highly heritable and polygenic and where impulsive behavior or lack of impulse control (behavioral response inhibition) are central to their symptomatic criteria. The first two behavioral phenotypes were two prevalent and complex primarily developmental disorders, attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) where lack of impulse control (BRI) are core manifestations of the disorders. The second two behavioral phenotypes were two severe complex behavioral phenotypes, borderline personality disorder (BPD) and schizophrenia, where lack of impulse control (BRI) arguably presents the most significant treatment challenges. Fifth, the literature on neuropsychological, neurophysiological, and neurobiological endophenotypes, with a focus on the above DSM behavioral phenotypes, provided an integration of the RDoC, endophenotypes, impulsivity and

BRI, behavioral phenotypes, and their operationalized measures. Sixth, the literature on neurocomputational studies (including studies that invoke artificial intelligence, machine learning, and deep learning artificial neural network predictive algorithms) represents an area of inquiry that can be informed by the findings of this study, particularly in the context of NDST as applied to RDoC enabled neural network dynamics. Neurocomputational studies frame a key application of the findings of this study and application for future research, using a reductionist approach to dimensionalize and decompose neurobiological and neuropsychological endophenotypes into deep endophenotypes to build better inputs (feature extraction and selection) for holistic emergent systems based on NDST and computational and behavioral neuroscience enabled neurocomputational dynamical models (diagnostic, differential, and digital twins) of impulsivity and deficits in impulse control (BRI) in a transdiagnostic regime.

Behavioral and Psychiatric Genetics Literature

Behavior is the phenotypic output of the brain. Behavioral genetics is the study of the role of genotypes on behavior (Knopik et al., 2017). Psychiatric genetics is a sub-field of behavioral genetics that focuses on the development of behavioral phenotypes (mental disorders or psychopathology; Ellenbroek & Yoon, 2016, Nurnberger & Berrettini, 2012; Schulz & McMahon, 2018). Consequently, psychiatric genetics focuses on the heritability of mental disorders. Between an average of 40% to 80% of the differences between phenotypes of mental disorders are attributable to differences in genotypes of individuals with these disorders (Hoehe & Morris-Rosendahl, 2018). Studies that seek to identify associations between given alleles or groups of alleles, either etiological or correlational, and behavioral phenotypes can provide critical information regarding the origin, early diagnosis, prevention, and amelioration of mental disorders. Further, the design and quality, accuracy (selectivity and specificity), precision, and

differentiability of measures used for such studies is of particular importance to quantify the heritability of behavioral phenotypes, a focus of this study.

Although the heritability of mental disorders is relatively high, the percentage of phenotypic variance that has been explained and elucidated by psychiatric genetic studies is extremely low (Fisch, 2022; Zaitlen & Kraft, 2013). This is known as the missing heritability problem and can be attributed to the methods (units of measure) used to identify and quantify genetic variants (polymorphisms or alleles), rather than the traditional methods used to determine heritability, which are distinct (Fisch, 2022). Missing heritability can be attributed to the difference between quantitative heritability and molecular heritability. Quantitative heritability studies seek to identify the liability of all genes on a behavioral phenotype. Molecular heritability studies seek to identify the liability of individual genes (specifically, alleles) on a behavioral phenotype. The missing heritability problem may simply be explained by the failure of molecular genetic studies to date to identify all alleles that contribute to genetic liability of a behavioral phenotype that are accounted for, in the aggregate, by quantitative genetic studies (Ferrera & Nurnberger, 2022; Knopik et al., 2017).

Psychiatric genetics studies (molecular heritability) used to identify and quantify specific genotypes most responsible for phenotypic variance among psychiatric disorders (behavioral phenotypes) comprise the group of psychiatric genetics studies that are a primary focus of this study. For example, candidate gene studies typically target either denovo identification of alleles associated with a particular behavioral phenotype, exploration of prognostic allelic indicators, or assessing the liability of a specific allele on a behavioral phenotype (David, 2021). Since candidate gene studies are based on *a priori* assumptions regarding associations between candidate genes and behavioral phenotypes, they are hypothesis testing methods of candidate

risk alleles (David, 2021). In contrast, genome wide associations studies (GWAS) are hypothesis generating methods (David, 2021). Genome-wide association studies (GWAS) interrogate the entire genome to identify primarily single nucleotide polymorphisms (SNPs) or copy number variants (CNV's), each of small effect, that collectively impart liability on a behavioral phenotype as a product of differences in their frequency distribution between clinical and neurotypical samples (Craig, 2012; Ferrera & Nurenberger, 2022; Uffeleman et al., 2021).

Polygenic risk scores (PRS), which interrogate summary statistics from GWAS studies to describe the accumulated risk (liability) of an individual for a behavioral phenotype as a product of the sum of individual risk alleles, can be used as a quantitative diagnostic tool for differential diagnosis of mental disorders. Several aspects of candidate gene, GWAS, and PRS in the context of NDST are key in the context of endophenotype research. First, while there are a finite number of genes, and a finite, albeit large, number of possible alleles (i.e., genotypes), there is an apparently infinite number of possible phenotypes (de Vienne, 2022).

Second, “there is no limit to the number of measurable or calculable phenotypes at all levels of biological organization and over the full range of spatial and temporal scales” (de Vienne, 2022, p. 155). From an NDST perspective, this means that phenotypic determination is spatially and temporally scale agnostic. Phenotypes can exist at the molecular level or at the behavioral phenotype level and everything in between using any unit of measure in RDoC or otherwise. Quantitative genetics and molecular genetics concepts can be applied across scales of phenotypic organization because most such intermediate phenotypes are also polygenic, whether express or latent (i.e., psychiatric markers or endophenotypes; de Vienne, 2022).

Third, a key determinant of the bounded scope of genotypes and apparently unbounded scope of phenotypes is pleiotropy (Fisch, 2022; Martin et al., 2019; de Vienne, 2022). Pleiotropy

is the concept where a given allele confers risk to multiple phenotypes (Fisch, 2022; Martin et al., 2019). Consequently, PRS are sensitive to pleiotropic influence in that individual SNPs or CNVs can impart liability on multiple phenotypes and is often a problem in GWAS and PRS (Fisch, 2022; Martin et al., 2019). However, this also presents an opportunity to decompose pleiotropic relationships by scaling down or decomposing phenotypes where pleiotropic influences may be bifurcated (differentiated or dimensionalized) or at least reduced (i.e., simplified). Thus, the often-apparent conflict between reductionist and deterministic research on emergent (NDST) complex systems may actually be reconciled, at least to some extent, by understanding that emergent phenomena can have reductionist etiology. The above are important suppositions to consider in light of the endophenotype literature.

Some authors have questioned the assumption that effect sizes and statistical power of genotypes contributing to endophenotypes are larger than that of genotypes contributing to behavioral phenotypes (Fisch, 2022; Flint & Munafo, 2007; Iacono et al., 2014). However, reports questioning this assumption often focus on particular endophenotypes, suggesting endophenotype selection, characterization, identification, or differentiation may be the issue, rather than the endophenotype concept itself, which includes identifying endophenotypes that can be subject to monogenic decomposition. Thus, monogenic decomposition and deep phenotyping may be a critical endgame in endophenotype research and was a key focus of this study, as discussed further below after discussion of endophenotype criteria and dimensional models.

Iacono et al. (2014) made several observations that were informative for this study and provided useful inferences. First, somewhat contrary to the endophenotype hypothesis, as was suggested by Flint and Munafo (2007), polygenic heritability of endophenotypes is not

necessarily simpler than for a related upstream behavioral phenotype. Second, the larger the missing heritability, the fewer risk alleles are known, since such alleles remain latent. Third, studies that focus on over selecting samples at the extremes for each endophenotype may improve results to identify candidate endophenotypes. This inference influenced the sampling and study design for this study. Fourth, for endophenotypes to achieve their potential as alternative targets for behavioral phenotypes, a balance must be achieved between given effects of each risk allele and sample size to optimize power to detect smaller effects.

The fourth inferential observation in the previous paragraph from Iacono et al. (2014) suggests decomposing endophenotypes to find a narrower set of risk alleles each with fractionally greater effect. For example, Ford (2014) suggested parsing the P3 endophenotype into its decomposed component parts that may be more genetically tractable as “endophenotypes for endophenotypes” (Ford, 2014, p.1344), what this study refers to as deep endophenotyping. Ford (2014) and Miller and Rockstroh (2013) are among those who suggest that decomposing endophenotypes can lead to stronger candidate endophenotypes.

Integration and Limitations of the Endophenotype Literature

Behavioral and psychiatric genetics is bridged to the DSM through the RDoC in the context of RDoC studies that include neurobiological and neuropsychological units of measure (endophenotypes) with the DSM nosology. This is accomplished by connecting a genetic correlate (risk allele) to a neurobiological correlate (e.g., fMRI enabled brain region [functional loci] or qEEG ERP component or waveform complex), which is in turn associated with a neuropsychological correlate (task measure or DSM agnostic psychological construct), and, ultimately, to a behavioral phenotype (DSM mental disorder). In the case of this study, this was accomplished with impulsivity and the putative executive function, behavioral response

inhibition (BRI), and their units of measure across neurobiological and neuropsychological domains.

Integrating the RDoC and behavioral and psychiatric genetics, Lenartowicz et al. (2010) made a critical ontological argument regarding executive functions, including behavioral response inhibition (BRI), fundamental to the premise of cognitive neuroscience, and thus behavioral neuroscience— that is, to map cognitive functions (cognitions), and thus behavior (motor actions), onto their neural substrates (neurobiological correlates)— that each cognitive and behavioral construct, such as BRI (i.e., a candidate endophenotype) and each uniquely measurable facet of that construct, should map onto a unique neural substrate (neurobiological correlate). However, McKenna et al. (2017) conducted a meta-analysis that concluded that neurobiological correlates rely on the structure of neuropsychological tasks that implicate different systems (endophenotypes) that the literature does not distinguish. While neurobiological correlates should map uniquely to differential endophenotypes, and in turn, cognate behavioral phenotypes, validation of this concept has been evasive.

In the over five decades since the endophenotype concept was introduced to psychology (Gottesman & Gould, 2003), endophenotypes have fallen short of simplifying studies of links between genotype and behavioral phenotype and have been questioned as viable units of study (Jonas & Markon, 2014). Similarly, studies of the construct of impulsivity as a putative endophenotype have been so inconsistent or demonstrated weak or non-repeatable associations with genotypes or behavioral phenotypes as to suggest that impulsivity may not be a construct at all, let alone an appropriate candidate endophenotype (Stahl et al., 2014; Strickland & Johnson, 2021). However, the issue may not be a problem with the endophenotype concept or whether impulsivity is a viable putative endophenotype, but a problem of scale (dimension) and of

appropriate endophenotype selection and its method of measurement where impulsivity and BRI and their facets are often confounded, and their measures also confounded across those constructs and their facets. Even the RDoC itself is not immune from confounding constructs and subconstructs and their measures. For example, the RDoC matrix confounds impulsivity with response selection and inhibition/suppression and suggests that measurements of impulsivity/inhibition include self-report and laboratory behavioral measures, without addressing impulsivity facets or which measures best measure those facets (NIMH, 2023).

Impulsivity and Behavioral Response Inhibition

Impulsivity can be described as a highly heritable stable personality trait or a dynamic state that comprises an urge to act (i.e., an impulse towards motor activity) and a lack of behavioral response inhibition to suppress the urge (Beauchaine et al., 2017; DeYoung & Reuter, 2016). Although impulsivity is often considered dysfunctional, it need not always be considered a dysfunction when temporal constraints or considerations derisk lack of premeditation and precognition. In other words, when the temporal benefits conveyed by skipping premeditation or precognition outweigh the risks, such that prepotency, automata, or habit may reduce those risks, impulsivity is functional and choice optimal rather than dysfunctional and suboptimal (Dickman, 1990). However, the focus of this study was dysfunctional impulsivity. Further, for the purposes of this study, a neutral definition of impulsivity may define impulsivity simply as behavior without forethought. This construct explicitly excludes cognitive impulsivity, a product of unique neural predicates and consistent with the motor focus of this study.

Impulsivity and compulsivity are arguably orthogonal. However, they merge at deficits in behavioral response inhibition (BRI [disinhibition]; Guo et al, 2017; Demetrovics et al., 2022; Fineberg et al., 2014; Naguy & Naguy, 2022; Sanchez-Kuhn et al., 2017). The merger of two

orthogonal constructs at BRI highlights the potential for BRI and its facets as putative endophenotypes. Impulsivity is often considered reward driven and risk-seeking and compulsivity relief driven and harm-avoiding (Demetrovics et al, 2022; Fineberg et al., 2014; Guo et al., 2017). Indeed, each often present as co-morbid intra-disorder deficits within several DSM mental disorders, including autism spectrum disorder and ADHD (Naguy & Naguy, 2022; Tzagarakis, 2022) and in co-morbid inter-disorder deficit occurrences, such as between ADHD and autism spectrum disorder (ASD; disorders with impulsivity as core deficits) and Tourette syndrome (TS) and obsessive-compulsive disorder (OCD; disorders with compulsivity as core deficits; Tzagarakis, 2022; Yang et al., 2021). Since disinhibition (deficits in behavioral response inhibition) lies at the nexus of impulsivity and compulsivity, BRI and its facets may serve as putative differential endophenotypes of either impulse control disorders and compulsivity disorders under the so-called mediational index model and liability index models.

Impulsivity is Not a Unitary Construct. Impulsivity is a strong candidate for identification of decomposed endophenotypes that comprise it. Many definitions of impulsivity are distinct and orthogonal to each other (Cyders, 2015). Such definitions often describe impulsivity as a trait or state. Other definitions characterize impulsivity in terms of a choice, attention, non-planning, cognition, or motor action. Each of these distinctions can be described as a type, sub-construct, facet, feature, component, factor, level, or variable of the broad construct of impulsivity. Each can also be considered constructs in their own right, with sub-types, facets, features, components factors of variables of their own or of each other.

Trait and State Impulsivity. Trait impulsivity (impulsive personality) is a latent longitudinally and temporally stable and consistent highly heritable personality trait and marks a facet of temperament that predicts one's reactions to day-to-day perturbations to one's

environment (Buhler et al., 2023). State impulsivity, also called behavioral impulsivity, is an ephemeral phase transition towards a dysregulated response to an internal or external stimulus, including through behavioral disinhibition (Buhler et al., 2023). Where trait impulsivity is the focus of self-report measures, state impulsivity is the focus of laboratory behavioral measures (Muele, 2013; Nguyen et al, 2018). State impulsivity thus implicates behavioral response inhibition, which implicates self-control, itself a facet of self-regulation and cognitive control (Nigg, 2017).

State impulsivity applies to the here and now and is more sensitive to environmental conditions in the moment, while trait impulsivity is more innate, focusing on stable traits comprising impulsivity (Barnhart & Beulow, 2017). Trait impulsivity can be characterized as a global tendency to be impulsive, as a lifelong temperament that favors impulsive action while state impulsivity can be characterized as a dynamical local sensitivity to impulsive action (see van Baal et al., 2022). In other words, one's tendency to be impulsive may be regulated by one's temporal in-the-moment sensitivity to transition from a base level of inhibition to partial or complete disinhibition. It can be measured either as a discrete phase transition from an inhibited to a disinhibited state or as a continuous phase transition from inhibition to increasing disinhibition. This latter aspect is one of magnitude of disinhibition or magnitude, intensity, or severity of impulsivity (van Baal et al., 2022). Put another way, the concept that impulsivity symptom intensity can be a product of sensitivity to triggers is similar to the concept put forth by Miskewicz et al. (2022) for borderline personality disorder (BPD) that stable personality traits (e.g., trait impulsivity) predict the perception of trigger intensity, which, in turn, predict symptom intensity (e.g., state impulsivity).

As noted below, BPD patients have higher impulsivity levels than even ADHD patients, which have higher levels than in other disorders. The discussions in this chapter of the types, sub-constructs, factors, and components of impulsivity, coupled with the presence of trait and state impulsivity, in light of sensitivity to activation, begin to suggest that the symptom intensity in BPD, ADHD, ASD, and schizophrenia may be explained by the compounding presence of various types (and facets and factors) of impulsivity in these patients (behavioral phenotypes). For example, a patient with one of these disorders may have both high levels of trait impulsivity and state impulsivity (or high levels of selected factors or facets of each), and high levels of choice impulsivity, motor impulsivity, cognitive impulsivity, attentional impulsivity, and/or non-planning impulsivity in different distinctly measurable differentiable discrete combinations. However, motor impulsivity due to deficits in BRI is arguably the operational symptomatic embodiment of a plurality of distinct forms of impulsivity. Hence it was the focus of this study. In other words, perhaps other forms of impulsivity can upregulate the frequency or intensity of motor impulsivity (a form of state impulsivity or behavioral impulsivity) or both. Pathological motor impulsivity (impulsive action) thus can be described as the observable pathological maladaptive externalized or internalized action, or reaction to a trigger or stimulus, that elicits a negative endogenous or exogenous environmental reaction or consequence and is optimally measured by the BIS-11 self-report measure of trait impulsivity and the go/no-go and stop signal tasks of state impulsivity (Chowdhury et al., 2017).

Cognitive and Motor Impulsivity. Cognitive impulsivity can be defined as one's myopic inability to properly balance the pros and cons of immediate versus future choices (Arce & Sansisteban, 2006). While cognitive impulsivity is a narrower construct than impulsivity, it is broader than choice, attentional, and non-planning impulsivity, each of which can be argued to

be facets of cognitive impulsivity (Barreno et al., 2019). Choice impulsivity is poorly correlated with motor impulsivity and even orthogonal to it (Hamilton et al., 2015; Wang et al., 2016).

Motor impulsivity (rapid-response impulsivity) is a facet of trait impulsivity and the focus of this study. It is the observable form of impulsivity. It is an act, a motor action that can be a product of other, latent forms of impulsivity, such as choice impulsivity and cognitive impulsivity, or can symptomatically exacerbate their impact. At the neuropsychological level, authors such as Bakhshipour et al., (2020) have observed marked differences in laboratory behavioral measures of motor impulsivity between ADHD patients and normal controls with ADHD patients showing marked differences in motor impulsivity but not choice impulsivity. This is an example of the potential unique transdiagnostic importance of motor impulsivity versus other types of impulsivity.

Behavioral Response Inhibition (BRI). Behavioral response inhibition (BRI) is the ability to suppress a prepotent or habitual response, including both motor actions and higher-order responses (such as thoughts, memories, or emotions) and is therefore critical to the ability to stop or suppress rapid, automatic behaviors in response to goals or environmental contingencies (Congdon et al., 2010, p. 2).

While impulsivity is affirmative behavior, inhibition implies the opposite, a means to keep impulsivity in check, yet deficits in BRI are often treated as synonymous with impulsivity in the literature (Stahl et al., 2014). Using Barkley's theory of inhibitory deficits, BRI can be decomposed into prepotent response inhibition, prepotent response extinction, and interference control. Prepotent response inhibition (action restraint) is inhibition of a primed prepotent (e.g., habitual or automatic) response to a thought (endogenous cognition) or to an external stimulus (Eagle et al., 2005; Ettinger et al., 2018; Korolczuk et al., 2018; MacKillop et al., 2016; Miyake

et al., 2000; Schachar et al., 2007; Sebastian et al., 2013; Shi et al., 2020; Sperl et al., 2021; Stahl et al., 2014; Tiego et al., 2018; Wessel, 2017). Prepotent (response) extinction (action cancellation), a term created for use with this study, is inhibition of an ongoing response to an internal cognition or to an external stimulus, long enough to determine whether it is appropriate to continue to respond (Afonso et al., 2021; Schachar et al., 2007; Sebastian et al., 2013; Sperl et al., 2021; Stahl et al., 2014). Interference control derives from cognitive rather than motor impulsivity with distinct neural substrates and was not a focus of this study.

Impulsivity Across Behavioral Phenotypes. From an RDoC perspective, variation in impulsivity, whether by token of magnitude or variation in its facets, components, factors, or features, accounts for covariation among DSM disorders that implicate it (Beauchaine et al., 2017). Impulsivity is central to essentially all externalizing disorders in the DSM, many of which co-occur due to that common thread. Impulsivity is particularly salient to four such disorders: ADHD, ASD, schizophrenia and borderline personality disorder (BPD).

Perhaps no other DSM mental disorder is considered more synonymous with impulsivity than attention deficit hyperactivity disorder (ADHD). However, as noted above, impulsivity and compulsivity are often considered two sides of the same coin that merge at deficits in behavioral response inhibition. A product of that merger is that ASD and ADHD are often comorbid. Consequently, deficits in behavioral response inhibition (lack of impulse control/lack of inhibitory control) are considered a central executive dysfunction of ASD (Hlavata et al., 2018; Schmitt et al., 2019; Velasquez et al., 2017). These deficits lead to marked impulsivity among the ASD population that have very negative consequences resulting from emotional dysregulation, self-injury, impulsive anger, and a form of cognitive impulsivity (Hlavata et al., 2018; Uzefovsky et al., 2016).

A deficit in BRI is also the operational embodiment of the severe cognitive dysfunction in schizophrenia (Enticott et al., 2008; Ethridge et al., 2014; Hoptman et al., 2018; Lau et al., 2022; Nanda et al., 2016; Ouzir, 2013). So severe is impulsivity in schizophrenia that deficits in BRI resulting in impulsivity are greater in schizophrenia than in ADHD (Hoptman et al., 2018). This dysfunction often results in externalized impulsive anger, aggression, violence, and internalized suicidal behavior as patients with schizophrenia react with motor action to their psychotic delusional episodes, hallucinations, and paranoia with want of forethought (Hoptmann et al., 2018; Lau et al., 2022; Ouzir, 2013). Finally, among the Cluster B personality disorders, impulsivity is largely considered to be both the core clinical dysfunction and primary diagnostic marker of borderline personality disorder (BPD) as well as its key prognostic marker over time (Gunderson et al., 2018; Jacob et al., 2009; Linhartova et al., 2019; Links et al., 1999; Moeller et al., 2001; Mungo et al., 2020; Ruocco et al., 2021; Sebastian et al., 2013; Sellbom et al., 2017; Soloff et al., 2017; Svaldi et al., 2012; Wojciechowski, 2021). While, arguably, impulsivity is most often associated with ADHD, impulsivity in BPD is considered more severe than in ADHD (Cackowski et al., 2014; Linhartova et al., 2019; Mungo et al., 2020; Wojciechowski, 2021).

Neuropsychological Measures as Endophenotypes of Impulsivity and BRI

Both self-report and behavioral neuropsychological measures were used in this study as detailed in Chapter 3. The Barratt Impulsiveness Scale (BIS-11), a self-report measure, primarily measures higher order factors of motor impulsiveness, attentional impulsiveness, and non-planning impulsivity and six lower order factors (components or facets) of each (Patton et al., 1995). The go/no-go (GNG) task (Newman et al., 1985) measures the ability to inhibit a habitual prepotent response (action restraint) in the presence of a rare stop stimulus (Xia et al., 2020). Unlike with the GNG, where a habitual prepotent action must be inhibited prior to action

initiation, with the stop-signal task (SST; Lappin et al., 1966; Logan et al., 1997), the prepotent habitual action must be inhibited after it has already been initiated (action cancellation; Schachar et al., 2011). The SST uses a horse race model between completion of the action and cancellation of the action—that is, between response execution and response extinction (Schachar et al., 2011). Consequently, with the GNG, a prepotent response must be inhibited, and with the SST, a prepotent response already begun must be extinguished. For this reason, action cancellation (measured by the SST) was termed in this study as prepotent (response) extinction, to capture the fact that both measures deal with primed prepotent habitual actions.

Finally, the Wisconsin Card Sorting Test (WCST; Berg, 1948) is a neuropsychological laboratory behavioral measure (paradigm) of set-shifting and cognitive flexibility (Berg, 1948; Monchi et al., 2001). The WCST is also used to test, and serves as a proxy for, neurobiological function of the prefrontal cortex (PFC), particularly the dorsolateral prefrontal cortex (dlPFC), and related executive functions, as confirmed using various neuroimaging methods, including DTI and fMRI, (Lombardi et al., 1999; Monchi et al., 2001). When the WCST is used in studies with the BIS-11 self-report psychometric measure and GNG and SST laboratory behavioral measures (paradigms), as was the case in this study, it can help discriminate cognitive (choice) and motor impulsivity when one, but not the other is present. Using the RDoC framework, each unit of measure described above is a putative endophenotype and this process of better discrimination (dimensionalization) may be termed RDoC latent variable endophenotype decomposition (to assemble deep endophenotypes), which was a focus and goal of this study.

Neurocomputational Applications of This Study

A primary goal of this study was to inform variable inputs (including feature selection and downstream feature extraction and engineering) into neurocomputational models (including

digital twins) and studies. Neurocomputational models can describe a neurobiological system (the what), explain mechanisms of operation of a neurobiological system (the how), and even help explain why a neurobiological system operates in a certain manner (the why; Anderson, 2014; Moustafa, 2018; Sanchez, 2021; Sterratt et al., 2024). Neurocomputational models can also be divided into theory driven models and data driven (atheoretical) models. Theory driven neurocomputational models (using reinforcement learning or Bayesian optimal fitting or Bayesian causal modeling [BCM], for example) can be used to understand mechanisms (Huys et al., 2016; Khaleghi et al., 2022). Data driven atheoretical approaches (using machine learning and deep learning) can be used to find hidden clusters to create predictive models to diagnose and treat psychiatric disease (Huys et al., 2016; Khaleghi et al., 2022).

Computational and behavioral neuroscience concerns the development of neurocomputational models of neurobiological substrates of behavior or of behavioral systems with a neurobiological nexus (Anderson, 2014; Florez, 2012; Moustafa, 2018; Liu & Li, 2024; Wilson & Collins, 2019). Neurocomputational models thus explicitly implicate the RDoC's underlying premise and goals, incorporating NDST principals, by first modeling DSM agnostic systems and behavior, and then developing specific models of behavioral phenotypes (digital twins), a key goal of this study (Iglesias et al., 2017; Montague et al., 2012).

One cycle of study progression can be to first conduct empirical studies of specific aspects (model inputs) of a behavioral system (e.g., decomposed endophenotypes of BRI as in this study), use those empirically and mathematically selected features (inputs) to develop a neurocomputational model of the system, fit the model to real world data using AI, including machine learning and deep learning artificial neural networks; form a hypothesis informed by the model, test the hypothesis in empirical studies, feed results into an iterated model (including via

use of AI enabled reinforcement learning), and then apply or implement the model into translational research of behavioral phenotypes, and finally, build a model (a digital twin) of a behavioral phenotype (Abilkaiyrkyzy et al., 2024; Friston, 2023; Iglesias et al., 2017; Montague et al., 2012; Spitzer et al., 2023; Wang & Krystal, 2014).

Explicit Gaps In The Literature That Supported The Need For This Study

Much of the failure of RDoC endophenotype research arises from issues with the measures used (units of analysis or measure) and with identification of appropriate candidate endophenotypes along the continuum of those measures. Many of the gaps in the literature that this study was designed to fill derived from this observation. The literature has slowly, albeit inconsistently, acknowledged that impulsivity and its facets, are not unitary, and that different neuropsychological measures apply to different facets (Bhaijiwala, 2016; Eagle et al., 2008; Ettinger et al., 2018; Friedman & Miyake, 2004; Korolczuk et al., 2018; MacKillop et al., 2016; Raud et al., 2020; Shi et al., 2020; Stahl et al., 2014; Tiego et al., 2018). Arguably, however, the literature has not gone far enough, and similar dimensionality problems of impulsivity facets (or of inhibition/impulse-control) have surfaced at lower scales of study, with many of the same problems as those at higher scales (Afonso et al., 2021; Ettinger et al., 2018; Friedman & Miyake, 2004; Raud et al., 2020; Skippen et al., 2020; Stahl et al., 2014). Stahl et al. (2014) further note that lack of clearly defined facets (dimensions) of impulsivity and consensus on their measurement presents a gap in the literature that urgently needs to be filled. In addition, in discussing the limitations of their study and ideas for future studies, for example, Carlisi et al. (2017) suggested use of neuropsychological measures that better discriminate DSM behavioral phenotypes in the context of transdiagnostic (RDoC) correlates.

Wang and Krystal (2014) have also noted a need to fill the very gap this study was intended to fill. They noted that “there remains a hope that endophenotypes may be more precisely defined, measured, and related to the underlying biology” (Wang & Krystal, 2014, p. 643). Wang and Krystal (2014) observed that the historical unitary treatment of impulsivity and BRI (noting their transdiagnostic nature) is flawed and that each may be decomposed into processes (facets, components, factors, features) that can each serve as candidate endophenotypes. Wang and Krystal (2014) then posited that improved endophenotypes of impulsivity and BRI can then be used to develop theories from neurocomputational models as applied to both neurotypical and clinical populations and iterate model development to map onto specific behavioral phenotypes including ADHD, ASD, schizophrenia, and BPD, from models of DSM agnostic RDoC dimensionally framed psychological constructs of impulsivity and BRI.

Thus, there remains numerous problem methodological gaps in the literature as well as empirical and knowledge gaps. First, lower order facets of inhibition are not consistently measured by not only distinct neuropsychological measures, but also subscales of those measures, to identify more suitable candidate endophenotypes via stronger links to neurobiological correlates and/or behavioral phenotype. Second, task measures do not consistently discriminate facets so measures of neurobiological and neurophysiological endophenotypes (e.g., fMRI and EEG) do not consistently and reliably differentially map those facets. Fourth, tasks do not consistently discriminate facets, so fail to consistently differentially map onto behavioral phenotypes, if at all. Fifth, an empirical and knowledge gap, the literature has failed to test (or discriminate) whether subscales of self-report measures are better correlated with subscales of laboratory behavioral measures than higher order scales (factors) are correlated between self-report and laboratory behavioral measures. This final gap ties to previously

described poor correlation between self-report and laboratory behavioral measures in the literature (Barnhart & Beulow, 2017).

This study sought to address the above gaps and has numerous applications across the behavioral and psychiatric genetics, endophenotype, impulsivity, BRI, and neurocomputational literature, including explicit gaps in the RDoC, and development of neurocomputational models and tools using AI machine learning and deep learning, and further including as follows:

1. The RDoC may lack fully robust domains and constructs. This study intended to inform both aims.
2. The findings of this study can benefit the behavioral and psychiatric genetics literature by better discriminating and dimensionalizing facets of impulsivity and BRI such that it can more successfully identify credible risk alleles (candidate genes) identified by decomposing endophenotypes to close the gap of the missing heritability problem.
3. The findings of this study can also benefit the behavioral and psychiatric genetics literature by helping close the gap of missing heritability by improving the accuracy, precision, and discriminate validity of measures used in such studies, measures which are or can become candidate endophenotypes.
4. The findings of this study can benefit the behavioral and psychiatric genetics literature via the inference that can be made from the gaps in the literature: If the wrong (or a less optimal or applicable) measure is used to quantify a facet of impulsivity (or quantifies the wrong facet), or fails to differentiate distinct facets in a twin, adoption, or family study of impulsivity, then results of such studies may be

misleading or may overstate or understate the genetic liability of the construct or of its individual facets.

5. The findings of this study can benefit the behavioral and psychiatric genetics literature by identifying individual risk alleles that have relatively large effect compared to other risk alleles for a given behavioral phenotype, which should provide more optimal targets for psychopharmacological, behavioral, and psychotherapeutic interventions (Gorlov et al., 2011; O'Connell et al., 2022).
6. The findings of this study can benefit the behavioral and psychiatric genetics literature, by addressing a key aspect of identifying risk alleles, that is, improving or discriminating the coupling of the dyad between units of measure (under RDoC) and the individual endophenotypes they are used to quantify. This can be accomplished through a process of decomposing those endophenotypes to more fundamental component endophenotypes to comprise deep endophenotypes.
7. The findings of this study can also help resurrect the candidate gene literature in behavioral and psychiatric genetics. The NIMH removed individual genes from the Genes unit of analysis in the RDoC matrix due, at least in part, to the issue of small effect size of candidate genes, since such unit of analysis would list such candidate genes and, notwithstanding that GWAS studies are welcomed by the RDoC, that was still the case as of 2024 (NIMH, 2024). If studies, such as this study, can better discriminate endophenotypes associated with their genotypes, the effect size of given candidate genes may be improved to be acceptable for use in RDoC studies, although an RDoC study, such as this study, can also be used with traditional candidate genes studies.

8. The findings of this study can inform neurobiological endophenotypes directly. If certain neuropsychological measures (scales and subscales) can be better discriminate psychological constructs at one level, and facets of those constructs at another level, they (scales and subscales) may be strong candidate endophenotypes in their own right or may better inform other more upstream and neurobiologically primitive candidate endophenotypes (e.g., N2/P3 complex).
9. The findings of this study can also inform better discrimination of neurobiological endophenotypes directly. For example, no qEEG/ERP studies to date have examined N2/P3 amplitude or relative latencies using select outcome variables separately of each of the GNG, SST, or the WCST in groups bifurcated by trait motor impulsivity subscales of the BIS-11. This study aimed to identify neuropsychological and neurobiological (by proxy) endophenotypes related to these subscales and outcome variables that can then be incorporated into such studies to further and more discriminately characterize N2/P3 putative endophenotypes of BRI and its upstream implicated behavioral phenotypes. Such discrimination can be used to better inform studies of either N2 or P3 ERP components or the N2/P3 waveform complex in similar studies of behavioral phenotypes. For example, as discussed in the section in this chapter relating to endophenotype typing and decomposition, Ford (2014) suggested the decomposition of the P3 ERP component to better enable its discrimination and association with candidate genes for schizophrenia (candidate SNP alleles), which, due to gaps in the BRI endophenotype literature, has not been possible. This study provided one

opportunity to inform a more complex study similar to the model study in light of Ford (2014) with the decomposed (deep) endophenotypes of this study.

10. This study sought to decompose neuropsychological and neurobiological endophenotypes of behavioral response inhibition, which, as discussed previously, is a condition precedent to proper engagement of executive functions. The goal of such decomposition was to better inform the ultimate goal of endophenotype research: to identify risk alleles for a behavioral phenotype, by way of risk alleles for the endophenotype, and to identify the functional consequence of such risk alleles (Miller & Rockstroh, 2013). In the case of this study, endophenotypes for deficits in behavioral response inhibition can tie risk alleles to differential expressions of functional impulsivity for behavioral phenotypes.
11. The findings of this study can inform studies of facets of trait motor impulsivity and BRI that seek to quantify neurobiological and neuropsychological correlates in the context of genetic liability so as to operationalize more precise measurement of endophenotypes. The findings of this study can help identify narrower endophenotypes, represented by neurobiological and neuropsychological correlates, related to facets or subsets or more primitive endophenotypes of broader constructs, such as trait motor impulsivity and BRI.
12. The findings of this study can inform future studies based on the theoretical foundations of the RDoC and Barkley's theory of inhibitory deficits, and numerous other theories, including the basal ganglia model and dopamine transfer deficit theory, and the dynamic development theory. So, for example, this study was intended to inform studies that may test dynamic development theory implicating

NDST by first decomposing endophenotypes from a reductionist perspective, to improve the inputs into more complex studies of system dynamics.

13. The findings of this study can improve the ability of neuropsychological measures to discriminate facets of BRI and associate those measures with self-report measures of impulsivity or compulsivity, thereby helping to identify decomposed endophenotypes that are useful in discriminating both impulsivity and compulsivity and their downstream behavioral phenotypes. The findings of this study can also improve differential diagnosis of impulsive and compulsive disorders. Behavioral response inhibition is a more fundamental marker of both impulsivity and compulsivity and their dysfunctional maladaptive manifestations.
14. The findings of this study can also improve differential diagnosis of DSM disorders. While the common thread of impulsivity across a plurality of DSM disorders may make differential diagnosis more difficult, if deficits in impulse control can be decomposed to unique diagnostic markers or endophenotypes to increase their dimensionality, they may help improve differential diagnosis.
15. The findings of this study can further inform differential diagnosis of DSM disorders. For example, ADHD is potentially over diagnosed and its diagnostic criteria may indeed be too subjective to differentiate it sufficiently from baseline norms, particularly as to adults, to avoid potential overdiagnosis (Taylor et al., 2022). There is a need for both objective diagnostic criteria and finer stratification of its classification (Taylor et al., 2022). As another example, because of the plural symptomatic overlap between schizophrenia and BPD, if operational embodiments of impulsivity between the two can be distinguished by the findings of this study, it

may help improve differential diagnosis between them. Impulsivity may be the most treatable symptom of BPD (Gunderson et al., 2018). Better discriminating and characterizing it can inform more directed therapeutic targets against the unique impulsivity phenotypes in DSM disorders, such as BPD.

16. The findings of this study can address gaps and contradictions in the endophenotype literature. For example, while generally consistent with the low correlation between self-report and laboratory behavioral measures in the literature, it is possible that studies such as that by Aichert et al. (2021) and the literature they cited, which conclude that self-report and laboratory behavioral measures of impulsivity are poorly correlated, conflate the facets of trait impulsivity measured by the BIS-11 and behavioral response inhibition measured by the laboratory behavioral measures. The BIS-11 measures three higher order and six lower order factors of impulsivity and the laboratory behavioral measures each measure numerous factors. If these measures are dimensionalized and decomposed into their factors, facets, components, and features and each of those compared, it may be possible to identify stronger relationships between these decomposed factors and between self-report measures of trait impulsivity and laboratory behavioral measures of behavioral response inhibition or state impulsivity.
17. The findings of this study can also inform current institutional positions on impulsivity in the extant endophenotype literature. For example, the International Society for Research on Impulsivity (InSRI) compared the validity, reliability, and dimensional sensitivity of a plurality of laboratory behavioral measures of motor impulsivity and identified two neurobiologically and conceptually distinct subtypes

of motor impulsivity (rapid response impulsivity) that can be measured using laboratory behavioral measures: prepotent response inhibition and prepotent (response) extinction (used as a term for the purposes of this study; Chamberlain & Fineberg, 2015; Hamilton et al., 2015). These two facets directly map onto the first two facets of the three facets described by Barkley's theory of inhibitory deficits discussed previously. Among the measures evaluated, the go/no-go task was identified as a possible measure of prepotent response inhibition and the stop-signal task a measure of prepotent (response) extinction (Hamilton et al., 2015). The InSRI, however, did not identify which subscales of the above measures best segregate these two factors or optimize the discriminant validity of both measures (a goal of this study) and what neurobiological measures then correlate with those subscales (Hamilton et al., 2015). The findings of this study can help fill that gap.

18. The findings of this study can improve the construct validity of neuropsychological measures. The literature discussed in this chapter has, on the whole, improved the construct validity of neuropsychological instruments by identifying particular instruments best suited to particular constructs. But it has done far less as to identify instruments scales and subscales that dimensionalize those constructs.

Consequently, if one can improve the construct validity of a neuropsychological instrument in the context of its ability to measure a facet of a broader construct, even if that compromises its content validity on the broader construct, it may be possible to better discriminate the genetic liability of the facet and improve its candidate endophenotype status.

19. The findings of this study can provide reductionist dimensionally decomposed empirically and mathematically selected features (decomposed endophenotypes comprising deep phenotypes) as inputs into studies that develop high-dimension neurocomputational models of impulsivity and BRI for specific behavioral phenotypes that take an emergent and wholistic NDST perspective.
20. NDST is implicit in the RDoC. The findings of this study can provide reductionist dimensionally decomposed empirically and mathematically selected features (decomposed endophenotypes comprising deep endophenotypes) as inputs for studies that develop high dimension neurocomputational models (digital twins) of impulsivity and BRI for specific behavioral phenotypes that take an emergent and wholistic NDST perspective. Indeed, this was a planned application of the the findings of this study. To repeat from the discussion in the NDST section of this chapter, a premise of this study was that decomposed endophenotypes can be used in neurocomputational studies of BRI and of behavioral phenotypes. Again, better inputs result in better outputs and neurocomputational models of complex neurobiological systems require more precise segregation and dimensionalization (i.e., decomposition of low dimensional data to high dimensional data) of system elements so as to better understand their interactions. For example, in a neurocomputational study by van Hulst et al. (2015) on BRI, the authors did not discriminate facets of BRI under Barkley's theory or ascribe the GNG to a facet rather than BRI (cognitive control) overall. This represents a gap in neurocomputational model studies that can be informed by the findings of this study to provide more discriminating features for model design. In fact, in discussing the

limitations of their study, van Hulst et al. (2015) noted that future studies would benefit from better discriminated task measures

21. Another way the findings of this study can inform neurocomputational studies is through the application of neurocomputational models of DSM behavioral phenotypes by providing so-called computational assays that can be mapped onto neuropsychological (behavioral) and neurobiological (neuroimaging, genetic etc.) data obtained from clinical and neurotypical populations and individuals, so as to inform differential diagnosis (Iglesias et al., 2017; Pauli & Lockwood, 2023). In that sense, neurocomputational studies using validated decomposed endophenotypes from this study, can then identify neurocomputational endophenotypes.

Chapter 3: Research Method

Statement of the Problem

The problem addressed by this study was that the endophenotype literature does not adequately characterize and segregate the dimensionality of the latent psychological constructs of impulsivity and impulse control (i.e., behavioral response inhibition [BRI]). The purpose of this quantitative quasi-experimental ex post facto study was to discriminate neurobiological and neuropsychological measures through assessing the relationships between subscales of the Barratt Impulsiveness Scale (BIS-11) for low and high trait motor impulsivity and subscales of three laboratory behavioral measures of BRI, the go/no-go task (GNG), stop signal task (SST), and Wisconsin card sorting test (WCST). This quantitative quasi-experimental ex post facto study had multiple dependent outcome variables and a dichotomous independent predictor variable comprising two groups (factor levels). Consequently, a one-way (one-factor) unpaired between subjects multivariate analysis of variance (MANOVA) was used to assess the differences among composite means of linear variates of a set of laboratory behavioral measures comprising dependent outcome variables from each instrument for each level for each study. A post-hoc independent samples *t*-test was conducted (Welch's *t*-test was conducted if any MANOVA assumptions were violated and quadratic regression to investigate a reaction time threshold for the GNG model), if results were statistically significant, to identify the source of the differences and thus, to identify novel decomposed endophenotypes, including deep endophenotypes (Schumacker & Lomax, 2010). A Cook's leverage-residual (influence) sensitivity analysis was performed to improve statistical power and test the robustness of the models (Cook, 1977; Cook & Weisbert, 1982). A cross-model convergent analysis was conducted to identify the framework comprising a linear variate of candidate decomposed deep

endophenotypes across all models that exhibited the best power-parsimony combination for AI neurocomputational applications. The following sections of Chapter 3 include research methodology and design, alternative methodologies considered, population and sample, appropriateness of sample, materials or instrumentation, operational definitions and variables, study procedures, data collection and sampling procedures, inclusion/exclusion criteria, study design, data collection procedures, data analysis, assumptions, limitations, delimitations, ethical assurances, and summary.

Research Methodology and Design

The nature of this study was that of a quantitative study following the Research Domain Criteria (RDoC) promulgated by the National Institute of Mental Health (NIMH) division of the National Institutes of Health (NIH; see Chapter 2). RDoC studies must be (a) quantitative, (b) largely explicitly or implicitly premised in both behavioral neuroscience and the endophenotype hypothesis, (c) transdiagnostic, in that they implicate and cut across multiple DSM behavioral phenotypes, although they can inform specific DSM behavioral phenotypes, (d) implemented dimensionally across units of analysis (measures of brain function) and across neurobehavioral constructs (under domains, including subconstructs), and (e) implicate neurobiological correlates of transdiagnostic endophenotypes (Hakak-Zargar et al., 2022; NIMH, 2023).

Like this study, RDoC studies can also explicitly focus on self-report and behavioral measures. Dr. Sarah Morris, associate head of the RDoC unit of the National Institute of Mental Health, has stated that “[i]t is possible to do an RDoC informed project using only self-report or behavioral measures, again, incorporating those ideas about dimensionality and not simply looking at one extreme of a disorder” (National Institute of Mental Health, 2015, 40:48). The design of this study also aligns with the so called seven pillars of the RDoC (Cuthbert & Insel,

2013; Morris et al., 2022). This study: is translational (Pillar 1) in that it uses a construct (impulsivity) quantified across multiple units of analysis; is dimensional (Pillar 2) in that it assumes and measures a range of normal to abnormal trait motor impulsivity and behavioral response inhibition; seeks to identify reliable and valid measures to dissect the heterogeneity of constructs and DSM behavioral phenotypes (Pillar 3) that can more differentially and discriminately inform DSM behavioral phenotypes; utilizes a novel research design and non-clinical sampling (Pillar 4) to elucidate data driven behavioral phenotypes; uses integrative methods of measurements (Pillar 5) across neurobiological and neuropsychological behavioral and self-report classes; focuses on neurobehavioral constructs (Pillar 6) including impulsivity and behavioral response inhibition to inform differential diagnostic DSM regimes; and is designed to inform the evolution and categorization of RDoC domains (Pillar 7) by better discriminating motor impulsivity and behavioral response inhibition from other forms of impulsivity and behavioral response inhibition (Cuthbert & Insel, 2013; Morris et al., 2022).

A quantitative study design is appropriate because the associations that were determined by this study were empirically measurable and could be quantified with a measure of precision. The study design was quasi-experimental because non-probability convenience sampling was used, group membership was not random, and not all confounding variables controlled (including the presence of latent variables; Leedy & Ormrod, 2013). The study comprised an ex post facto design, in that the independent dichotomous predictor variable of high or low motor impulsivity, as measured by trait motor impulsivity subscales on the BIS-11, was a pretest variable and not applied or manipulated in the study (Leedy & Ormrod, 2013).

This study included three categories of measurements, (a) a psychometric self-report measure of trait impulsivity, with a focus on measures of self-reported trait motor impulsivity,

(b) a laboratory behavioral measure used as a proxy for neuroanatomical locus and neurofunctional dynamics (a neurobiological correlate) related to disinhibition (lack of impulse control), and (c) laboratory behavioral measurements of state motor impulsivity and behavioral response inhibition (neuropsychological correlates). As a pretest measure to determine experimental and control groups, initially, male participants ages 18-34, and after pilot testing and IRB approval to modify the participant pool (results of which were included in the analysis) male and female participants ages 18-40, completed the BIS-11 self-report questionnaire on-line via a Qualtrics enabled and hosted gateway through a forwarding link to Millisecond Software's Inquisit web portal and outcome measures on the BIS-11 subscales relating to trait motor impulsivity were used as the criteria for grouping of treatment and control groups. Each participant was then administered (i) the WCST as a measure of neuroanatomical function that relates to behavioral response inhibition and (ii) two laboratory behavioral measures (the GNG and the SST) of behavioral response inhibition (state impulsivity) that putatively or theoretically test at least two facets or phase states of trait impulsivity.

In order to determine the association between trait motor impulsivity and multiparametric differential response inhibition endophenotypes, study participants were divided into treatment and control groups along measures of trait motor impulsivity using the BIS-11 instrument. The size of the sample as well as the distribution of sampling groups (via convenience sampling) helped ensure reflection of the population within the limitations of convenience. Although ethnic diversity may have been established from a purposive sampling perspective, that independent variable was not controlled. The design of this study was quasi experimental in that associations for study were empirically measured, but not all confounding variables were controlled, some were latent, and sampling and group membership was not random (Leedy & Ormrod, 2013).

To address and align with the problem that the endophenotype literature does not adequately characterize and segregate the dimensionality of the latent psychological constructs of impulsivity and impulse control (i.e., behavioral response inhibition [BRI]), the study comprised an ex post facto component with an independent dichotomous predictor variable of a trait motor impulsivity subscale of the BIS-11 self-report questionnaire (Leedy & Ormrod, 2013). Each subject was exposed to an ex post facto pretest condition of dichotomous BIS-11 outcome measure for Factor I and Factor II motor impulsivity, a self-report measure, using the top and bottom quartile Factor I subscale scores to ensure discrete categorical segregation and sensitivity. This provided a basis of measurement for correlation between the high or low BIS-11 scores of motor impulsivity as independent predictor variables for laboratory behavioral assessment outcome measures suggested by the literature to be associated with behavioral response inhibition, motor impulsivity, and their neurobiological correlates, which were the testing/treatment conditions. This approach implemented the purpose to discriminate neurobiological and neuropsychological measures through assessing the relationships between subscales of the Barratt Impulsiveness Scale (BIS-11) for low and high trait motor impulsivity and subscales of three laboratory behavioral measures of BRI, the go/no-go task (GNG), stop signal task (SST), and Wisconsin card sorting test (WCST).

This design also aligned with the research questions. Each primary research question corresponded to a model of one of the laboratory behavioral measures of this study, which are among RDoC units of analysis. Each research question also had three sub-questions to support post hoc analysis of each dependent outcome variable comprising a subscale of each laboratory behavioral measure. Thus, each of the main research questions asked whether linear variates of three sub-scales (facets, components, features, factors) of each laboratory behavioral measure

differed between the dichotomous high and low groupings of BIS-11 subscales for trait motor impulsivity. Each post hoc analysis then answered each sub-question, namely, which sub-scale (dependent variable) associated most strongly with differences in BIS-11 trait motor impulsivity subscale scores.

While the go/no-go (GNG) and stop-signal tasks (SST) were the laboratory behavioral measures chosen for this study to measure the first two facets of Barkley's trivariate classification of behavioral response inhibition (BRI), other measures from the literature were considered. For example, the flanker task and Conner's continuous performance test (CCPT) were both considered (see Chapter 2 for a description of these tasks and other measures used in the literature). The flanker task was favored over the CCPT as it has a time delay component the CCPT does not have. The Stroop task was also considered. However, these measures were deemed not the best measures of motor impulsivity and Barkley's first two facets of behavioral response inhibition that were the focus of this study (Braunstein, 2014; Markovska-Simoska & Pop-Jordanova, 2017; Nash et al., 2013; Shahaf & Pratt, 2013; Tye et al., 2011).

The approach to addressing and aligning with the problem stated above sought to develop a nomological network of the dimensions of motor impulsivity as a latent variable through observational instrumental sub-measures that segregate those dimensions, a process referred to for the purposes of this study as RDoC latent variable endophenotype decomposition. This approach was consistent with RDoC's top-down approach. Such decomposed endophenotypes can also inform research on so called phenologs, which are orthologous phenotypes (or endophenotypes) that can inform differential research of DSM behavioral phenotypes (de Vienne, 2022).

Decomposed endophenotypes (deep endophenotypes) can also be used as more precise, informed, directed, aligned, and appropriate targets for study in broader RDoC studies that include direct neurobiological measures, including combinations of genotyping and neuroimaging and neurophysiological measures, as well as instrumental paradigm measures of behavioral phenotypes (see discussion, of generic model study in Chapter 2). Another potential use of decomposed and deep endophenotypes is as better segregated and discriminated inputs for machine learning and AI neurocomputational models (digital twins) of behavioral phenotypes used in computational psychiatry (see Chapter 2) to aid in differential diagnosis and characterization, a key goal of this study.

Alternative Methodologies Considered

RDoC studies typically focus on top-down quantitative designs and measures (Cuthbert, 2022; Ross & Margolis, 2019). Such RDoC designs include neurocomputational methods via computational psychiatry (Cuthbert, 2022; Ferrante et al., 2017; Pauli & Lockwood, 2023; Stephan & Mathys, 2014). In fact, neurocomputational methods now represent a priority for RDoC to enhance “the ability to define psychophysiological constructs validated by quantitative analyses of relationships among various measurement systems” (Cuthbert, 2022, p. 5). This is particularly the case for the development of neurocomputational models (digital twins) of DSM behavioral phenotypes (Cuthbert, 2022). Such neurocomputational models are the type of studies this study intended to provide inputs for in the form of decomposed endophenotypes for models of the four behavioral phenotypes discussed in Chapter 2. In light of RDoC’s structure, alternative methods considered were primarily quantitative. However, qualitative methods that help form theory can also inform downstream quantitative methods. These methods are also discussed first.

Alternative Qualitative Methods Considered. Since this study was premised by an RDoC and behavioral neuroscience foundation and intended to be applied to computational and behavioral neuroscience, it did not lend itself to qualitative methods. However, qualitative methods have been used to study the constructs (impulsivity and behavioral response inhibition) and behavioral phenotypes of this study and can inform quantitative RDoC studies. For example, grounded theory is a very rigorous and robust qualitative methodology designed to produce a formal and substantive theory of a particular social or behavioral construct (Nathanial, 2021). Grounded theory can be used to develop a theory regarding ADHD, for example, and impulsivity specifically, that can then be tested empirically in a quantitative RDoC study.

Castellan (2010) aptly compared quantitative and qualitative research as an epistemological contrast of “quantitatively professing an objective truth and a single reality or qualitatively promoting a subjective truth and multiple realities” (p. 2). One need not determine that one is better than the other for either the study of impulsivity and behavioral response inhibition or behavioral phenotypes like ADHD, ASD, schizophrenia, or BPD. Arguably, different theories of ADHD (or of other behavioral phenotypes) and psychological constructs like impulsivity can represent multiple possible realities, each of which can be tested to find one truth. Arguably, quantitative and qualitative research are complementary.

Grounded theory and phenomenology (another rigorous qualitative method) studies, for example, where impulsivity appeared imbedded among key themes, include the study of borderline personality disorder (BPD; Spodenkiewicz et al., 2013; Wasmuth et al., 2020) and ADHD (Brinchmann, 2014; Harazni & Alkaissi, 2016). Themes related to deficits in behavioral response inhibition include a phenomenological study of cognitive control that identified a thematic connection with hopelessness (Saunders et al., 2015). In each case, the participants

provided themes from which to base theory or organize phenomena. Development of these themes were informed by the experience of the researchers in sample selection and study design more so, it seemed, than one finds in quantitative studies, illustrating the importance of researcher experience in designing and implementing such studies. Consequently, while qualitative methods were not considered for this RDoC quantitative study, they can, nonetheless, help develop theories that can be empirically tested in RDoC studies, including neurocomputational studies.

Quantitative Methods Considered. Various quantitative designs were considered for this study based on a review of the literature. Most quantitative studies that involve endophenotypes of impulsivity and behavioral response inhibition that were reviewed are variants of ex post facto research designs. Typically, a study will have a control group (neurotypical or clinical) that comprises, for example, genotype negative control subjects for an allele implicated in impulsivity or behavioral response inhibition, and a treatment group of genotype positive subjects. Subjects then undergo one or more or a combination of neurophysiological measures (fMRI or qEEG) and self-report and laboratory behavioral instruments. Other studies provide for dichotomous groups using psychometric or laboratory instruments rather than genotyping. This latter type of study is the general type of study of this study.

Certain non-RDoC studies focus on clinical samples to identify differential endophenotypes. Kelly et al. (2021), for example, studied prepotent response inhibition in a group of 58 subjects with autism spectrum disorder (ASD) and 63 controls ages 5-29 using a combination of the stop-signal task (SST) and the antisaccade task. The authors concluded that the results indicated deficits in prepotent response inhibition implicated frontostriatal neural

networks (Kelly et al., 2021). Susana et al. (2021) studied prepotent response inhibition in a group of 28 Alzheimer's patients and a control group using electroencephalography (EEG) while the subjects completed the go/no-go (GNG) task. The authors used a pretest independent dichotomous predictor variable of the top and bottom quartiles (a sampling similar to that of this study) in a measure of subjective memory complaints. The endophenotype was the N2-P3 waveform complex (see Chapter 2 for a discussion of these endophenotypes). Ruocco et al. (2021) conducted a study to identify endophenotypes of response inhibition in a clinical sample of borderline personality disorder (BPD) in 86 probands as a treatment group, 60 relatives, and 83 controls. The subjects underwent functional near-infrared spectroscopy (fNIRS) at the prefrontal cortex (PFC) while they completed the go/no-go task. The endophenotype was PFC activation. Li et al. (2021) studied both prepotent response inhibition and interference control (two facets of behavioral response inhibition) in a clinical sample of 41 patients with major depressive disorder (the treatment group) and 39 controls using the stop-signal and flanker tasks. The goal of the study included differential diagnosis where response inhibition was implicated.

Other studies, for example, focus on neurotypical populations to identify behavioral phenotype agnostic endophenotypes of behavioral response inhibition. Afonso et al. (2021) studied behavioral response inhibition (BRI) in 30 undergraduate students ages 18-39 using a combination of the Stroop task and the stop-signal task (SST) to compare interference control with behavioral response inhibition. Fehring et al. (2021) used a sham-controlled and cross-over repeated-measure design to study the efficacy of transcranial direct current stimulation (tDCS) on the dorsolateral prefrontal cortex (dlPFC) of a sample of 73 participants using the stop-signal task (SST).

This study design was selected to conform with RDoC principles. It was particularly chosen to focus on associations between trait motor impulsivity and state motor impulsivity and facets of behavioral response inhibition. Later studies can then build upon the improved segregation of facets of self-report and laboratory behavioral measures of impulsivity and behavioral response inhibition (decomposed endophenotypes) by adding additional measures. Such additional measures include neurophysiological and neuroimaging measures, such as functional magnetic resonance imaging (fMRI), quantitative electroencephalography using event related potentials (qEEG/ERP) or functional near infrared spectroscopy (fNIRS). Each of the forgoing additional measures are discussed in detail in Chapter 2. Other measures include measures of DSM behavioral phenotypes such as the Minnesota Multiphasic Personality Inventory (MMPI-II) or the Millon Clinical Multiaxial Inventory (MCMI-IV). Further, as discussed above and in detail on Chapter 2, neurocomputational implementations of the above were a critical endgame for the findings of this study, including neurocomputational models (digital twins) of the four behavioral phenotypes discussed in Chapter 2: attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), schizophrenia, and borderline personality disorder (BPD).

Population and Sample

The study population comprised adults ages 18-40 (revised from adult 18-34 yr old males after IRB approval following pilot testing) from the general population (GenPop) Qualtrics panel of participants. While these participants were not representative of the general population, this study contemplated that if back-up sampling methods were used (they were not), cluster sampling may have improved ethnic and demographic distribution. Qualtrics also recruits or aggregates its research panels to maximize ethnic and sociodemographic diversity, but this was

not controlled for in this study. This sample also represented the largest cohort of participants in the Qualtrics panel from a convenience perspective, because it included university students who commonly engage in such research panels. The sample and sampling method was chosen to maximize the spread between high trait motor impulsivity and low trait motor impulsivity groups to increase study power and sensitivity to measurable differences and differentiation across subscales of both self-report and laboratory behavioral measures. The sample was also chosen to better align consistent and correlated outcome measures and minimize the confounding effects of sex and age across RDoC units of measure.

Presence of DSM Diagnosis. Participants were screened but not excluded for DSM diagnosis, with a focus on externalizing disorders, and were generally expected to represent similar prevalence of DSM psychopathology as the general population of 18–40-year-old males and females. Collection of one or more diagnosis was obtained for information purposes only, or for future reanalysis of the data, and not used in this study’s statistical analysis other than for reporting demographic information. Participants were provided the option to not provide a diagnosis, even if diagnosed, might have misreported a diagnosis, or failed to report co-morbid diagnosis, in addition to lacking a diagnosis where one could have been made. Consequently, the presence or identification of diagnosed or undiagnosed DSM psychopathology was not controlled for in this study and the sample was expected to include some latent measure of DSM psychopathology including ADHD, ASD, BPD, and, potentially, schizophrenia. As further discussed in the next section, a majority of this population likely had at least one psychiatric diagnosis, so controlling for or excluding it would not represent the general population.

Use of Psychotropic Medications. Further, this study did not control for the presence of psychopharmacologic interventions that decrease impulsivity or enhance behavioral response

inhibition, such as ADHD psychotropics or beta blockers. Consequently, medicated participants may have potentially been incorrectly placed in the control group of low trait motor impulsivity. More likely, such participants may have scored high on trait motor impulsivity, since they would self-report historical observations that included unmedicated state spaces, but scored low on laboratory behavioral measures of state motor impulsivity. This may have suggested a poor correlation between BIS-11 subscale scores and a laboratory behavioral measure subscale where such poor correlation was artificial and was caused by or materially influenced by a psychopharmacological intervention. While individuals on such medications were not excluded, use of certain medications were collected to enable future exploration of contribution of these confounding variables to the results and reported generally as part of demographic information, if appropriate.

Appropriateness of Sample

The initial target population under study was adult putative neurotypical males ages 18-34, later revised following pilot testing and IRB approval for revision to females and males ages 18-40. As mentioned above, DSM diagnosis was neither controlled for nor excluded. The initial population (24% of the male population) represented a gender (males) more likely to exhibit impulsivity in an age range that is more consistent with respect to impulsivity that also represents the age cohort commonly used to norm the measures used for this study (Chamorro et al., 2012). The 18-34 age range is also a common demographic seen in age range studies for groups characterized as young adults, including studies of impulsivity as representative of a stably impulsive population in young adults (Chamorro et al., 2012; Coley & Burgess, 2003; Morkem et al., 2020; Scott et al., 1999).

Further, of the four behavioral phenotypes of this study, both BPD and schizophrenia are not typically diagnosed until young adulthood while ADHD and ASD are typically diagnosed during childhood and often carry into young adulthood (Chamorro et al., 2012). Notably, roughly 83% of individuals who self-report high impulsivity have at least one psychiatric disorder, particularly externalizing disorders, compared to roughly 63% who self-report low impulsivity and the high impulsivity group is much more likely to have an Axis I disorder or a personality disorder (Chamorro et al., 2012). Borderline personality disorder, for example, is the psychiatric disorder most strongly predicted by impulsivity, by a wide margin, followed by narcissistic personality disorder and schizotypal personality disorder, with ADHD next highest (Chamorro et al., 2012; Franczak et al., 2024). The upper age range of the sample is particularly critical to capturing BPD and schizophrenia behavioral phenotypes to the extent they occur in the sample population.

Further, males ages 18-34 are far less likely to be taking cardiovascular medications, such as beta blockers, than males over 34, although that likelihood ratio would be expected to increase somewhat after extending the upper age to 40. Beta blockers, for example, could reduce impulsivity, particularly impulsive aggression, increase compulsivity, and otherwise alter the very dopaminergic and serotonergic systems that are implicated in impulsivity and behavioral response inhibition that are the focus of this study (Cojocariu et al., 2021). Beta blockers have been associated with increased incidence of obsessive-compulsive disorder, PTSD, and Parkinson's disease, all of which implicate dopaminergic neural network systems (Cojocariu et al., 2021). Not surprisingly, however, beta blockers are sometimes used to treat DSM disorders, although far less frequently than for cardiovascular disease, that implicate impulsivity and behavioral response inhibition, including schizophrenia, borderline personality disorder, and

ASD (Hauser et al., 2018; London et al., 2020; Prado-Lima, 2009). Consequently, even in the initial sample population of 18–34-year-old males, some participants may have been on such medications and those medications may have skewed results against a positive association between trait and state impulsivity. The use of such medications were screened for this study, but neither controlled nor excluded.

However, exclusion of females from the above initial sample did not reflect the general population. Most notably, BPD is more common in females in clinical populations by a factor of two to one (although of about equal prevalence in the general population), and schizophrenia tends to be diagnosed after age 25, and, finally, samples of 18-40 year old males and females are arguably more common in impulsivity studies using these four behavioral phenotypes than 18-34 year old males (Franczak et al., 2024; McGrath et al., 2008). However, the demographic portion of this study collected data regarding the use of beta-blockers, for example, along with age and gender so these may be controlled for in future reanalysis of the data. Consequently, the above supported the change in sample population for this study which should have captured more of these behavioral phenotypes and improve the generalizability of the data (see Chapter 4 for more details regarding this sampling modification).

Taking the above into account, the target population aligned with the problem that the endophenotype literature does not adequately characterize and segregate the dimensionality of the latent psychological constructs of impulsivity and impulse control (i.e., behavioral response inhibition [BRI]). This population also aligned with the purpose to discriminate neurobiological and neuropsychological measures through assessing the relationships between subscales of the Barratt Impulsiveness Scale (BIS-11) for low and high trait motor impulsivity and subscales of three laboratory behavioral measures of BRI, the go/no-go task (GNG), stop signal task (SST),

and Wisconsin card sorting test (WCST). Again, this population is the most commonly used to norm the laboratory behavioral measures used in this study and is a population was most likely to exhibit significant measurable impulsivity, particularly at the lower end of the age range.

Consistent with the characteristics of the population, it also aligned with the research questions. First, by helping to ensure measurable dichotomous groupings for BIS-11 trait motor impulsivity subscale scores. Second, by maximizing the likelihood of statistically significant measures of each impulsivity and BRI subscale for each behavioral measure used for each research question.

Sampling Method. There are two types of sampling methods that were appropriate for this study. The first was probability-based sampling (random sampling), which includes simple random sampling, cluster sampling, systematic sampling, and stratified random sampling (Fricker, 2017). In probability-based sampling, participants are selected based on a known probability of any member being selected, including via a stochastic or nearly stochastic process, with such participants having, practically speaking, essentially no say in participation (Fricker, 2017). The second was non-probability-based sampling (convenience sampling), which includes snowball sampling, quota sampling, and judgement sampling (Fricker, 2017). In non-probability-based sampling, the probability of a given participant joining the study cannot be determined in that each participant has a choice whether to participate (Fricker, 2017). Probability-based sampling methods are very difficult, resource intensive, and costly to implement for quantitative studies, such as this study (Fricker, 2017). In contrast, non-probability-based sampling methods are far less costly and easier to implement (Fricker, 2017). Further, pre-recruited research panel surveys, such as those used for this study via Qualtrics, are comprised of recruited, but self-selected, participants by convenience via a purposive sampling modality.

In light of the above, this study used purposive non-probability convenience sampling from the Qualtrics general population (GenPop) panel of United States participants (subject to exclusion criteria). Considering the large sample size required for sufficient statistical power and resources and cost of a purely random sample, this was the best sampling strategy for this study. Sampling was convenience based because Qualtrics maintains a panel of self-selected participants. All Qualtrics panels are pre-recruited and pre-screened by Qualtrics. Initial demographic information was also provided by Qualtrics. Qualtrics also handles compensation through a standard Qualtrics pre-set remuneration policy and management of panel membership and participation. Qualtrics recruits or aggregates membership for its research panels in such a manner to avoid or minimize common sampling errors and has procedures to ensure each research panel represents a broad demographic. If a back-up sampling method would have been used, colleges were local and accessible. Sampling was purposive because exclusion criteria was used. These included participants who could not complete all measures, who were left-handed, and those with significant eye impairments or color blindness.

Effect Size and Power

In quantitative studies, such as this study, sample size depends on effect size considerations and statistical power (Oravecz et al., 2011; Schumacker & Lomax, 2010). While statistical significance may enable rejection of a null hypothesis, practical significance is represented by the effect of an independent predictor variable on dependent outcome variables in the real-world population represented by the sample (Ellis, 2014; Kraemer & Blasey, 2016; Murphy et al., 2014). The magnitude of that effect is the effect size. As discussed in Chapter 2, issues with effect sizes (independent predictor variables with weak effect) predominate in both the behavioral genetics and neuropsychology literature. Odds ratios (for dichotomous

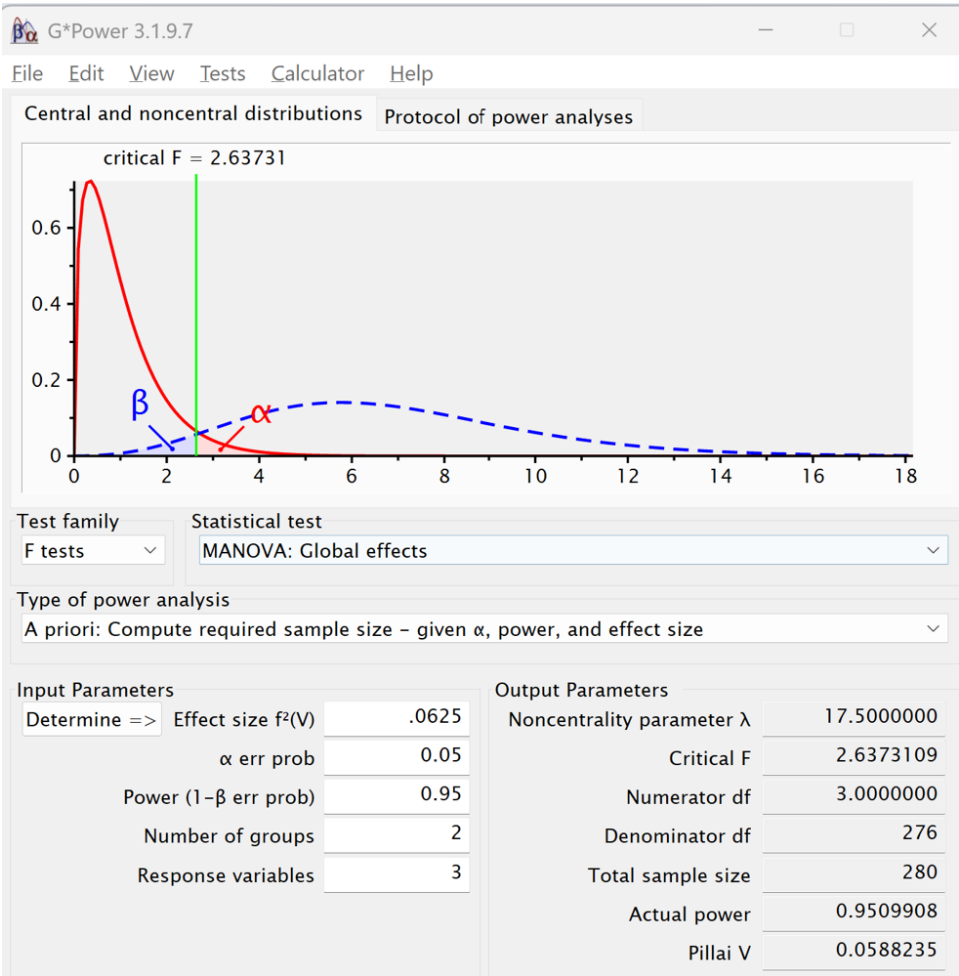
independent variables) and Cohen's d (for continuous independent variables) are common effect size statistics used in the endophenotype and impulsivity literature (Allen et al., 2009; Ellis, 2014; Murphy et al., 2014). Statistics related to correlation coefficients are also used to determine effect sizes, including Spearman's rank correlation, and Cohen's f or partial η^2 associated with F -tests used in multiple regression and MANOVAs, respectively (Ellis, 2014; Kraemer & Blasey, 2016; Murphy et al., 2014).

Statistical power represents the probability that a given measure or study will reject a false null hypothesis and correctly identify a genuine effect (Ellis, 2014; Kraemer & Blasey, 2016; Murphy et al., 2014). The larger a sample size, the less likely Type II errors (false negatives) will occur, the higher the power of the study (Ellis, 2014; Kraemer & Blasey, 2016; Murphy et al., 2014). Underpowered studies can miss meaningful effects (Ellis, 2014; Kraemer & Blasey, 2016; Murphy et al., 2014). Further, most studies set an alpha of $p < 0.05$ to represent the probability of Type I errors (false positives) with a power of .90 or .95 (90% or 95% of detecting a genuine effect; Ellis, 2014; Kraemer & Blasey, 2016; Murphy et al., 2014).

In light of the above, G*Power version 3.1.9.7 (March 2020) was used to calculate the sample size using the F tests test family, MANOVA Global effects (for linear composites of two or more dependent variables), for an *a priori* power analysis for two groups and three response variables for each of the three studies and $\alpha = .05$, a very conservative effect size of $f^2(V) = .0625$, and high power ($1 - \beta$ error probability) = .95 (Faul et al., 2007; Faul et al., 2009). As shown in Figure 7, G*Power analysis generated a preliminary minimum sample size of 280 for an actual power of .95. Further, the independent dichotomous predictor variable groups represented a pretest variable not applied or manipulated in the study comprising the top and bottom quartile scores of Factor I trait motor impulsivity on the BIS-11 instrument. Consequently, the total targeted

sample size was between 560-600 to permit sufficient powering of the top and bottom quartile scores.

Figure 7
*a priori G*Power Analysis*



Exclusion Criteria

Exclusion criteria, discussed in more detail below, included participants who could not complete all measures, left-handed participants, participants with poor hearing, English proficiency below seventh grade, and participants with significant eye impairments or color

blindness. Participants who also scored below a total score of 51 on the BIS-11 as potentially indicative of false, incomplete, or questionable reporting (Stanford et al., 2009) were reviewed for confirmation as to their motor impulsiveness subscale scores and excluded if those subscale scores were significant outliers.

Materials or Instrumentation

The proposed quantitative quasi-experimental ex post facto study was split into three studies. Each examined the differences among three dependent outcome variables comprising lower order subscales (three subscales per measure) of three laboratory behavioral measures and an independent dichotomous predictor variable comprising a self-report measure. Thus, there were four instruments total. The first, a self-report measure (the BIS-11), comprised high and low Factor I and Factor II trait motor impulsivity. Next, were two laboratory (neuropsychological) behavioral measures (go/no-go task and stop-signal task) that putatively measure prepotent response inhibition and prepotent response extinction, respectively. Finally, a laboratory (neurobiological) behavioral measure (Wisconsin card sorting test) that is a proxy for prefrontal cortical function. Operationally, the order of the three laboratory behavioral measures above was randomized for each participant.

The rationale for three studies, instead of one, related to the purpose of this study: to decompose behavioral response inhibition into two or more lower order facets to serve as differential endophenotypes for motor inhibition as related to trait motor impulsivity. The underlying theory applied (Barkley's Theory of Inhibitory Deficits; Barkley, 1997) assumes three facets for behavioral response inhibition (prepotent response inhibition, prepotent response extinction, and interference control). A literature search of virtually all instruments used for studies of impulsivity and behavioral response inhibition (see Chapter 2) resulted in two (the

go/no-go and stop-signal task) related to state motor inhibition that appear best for each facet that was a focus of this study (Raud et al., 2020). The Wisconsin card sorting test was appropriate for a third study as the sole putative neurobiological endophenotype, since the other two instruments served as neuropsychological endophenotypes. These instruments are often used in combination in the types of studies this study intended to inform and all four can be completed on-line in one sitting in under 30 minutes. Additional wording for the Inquisit implementation of each instrument was added to ensure each participant carefully read all directions.

Barratt Impulsiveness Scale Version 11 (BIS-11)

The Barratt Impulsiveness Scale version 11 (BIS-11) was used in this study to measure trait motor impulsivity and determine treatment and control groups, since this study sought to predict facets of behavioral response inhibition from trait motor impulsivity (instrument shown in Appendix C). Permission to use the BIS-11 for this study was provided by a license from Millisecond Software. The BIS-11 is considered the gold standard for measurement of trait impulsivity (Stanford et al., 2009). The original version of the BIS was developed by Barratt in 1959 based on a three-factor structure of impulsivity: attentional, non-planning, and motor impulsivity premised on his orthogonal treatment of anxiety and impulsiveness (consistent with the discussion in chapter 2 concerning the orthogonal nature of impulsivity and compulsivity; Stanford et al., 2009). The current 11th revision was developed in 1995 (Stanford et al., 2009).

The BIS-11 comprises 30 questions that measure six first order impulsivity factors (Factor I: attention, motor, self-control, cognitive complexity, perseverance, cognitive instability) that comprise three second order factor sub-traits (Factor II): non-planning impulsiveness (lack of premeditation or precognition), motor impulsiveness (action without thought), and attentional

impulsiveness (lack of the ability to concentrate; Coutlee et al., 2014; Patton et al., 1995; Stanford et al., 2009).

Responses to the questions are made via computer (or on-line via a portal) using a four-point Likert scale of rarely/never, occasionally, often, and almost always/always that are summed (scores range from 1-4 or 4-1 along the scale). The current version of the scale was normed against college students and compared to psychiatric inpatients and prison inmates for further validation (Vasconcelos et al., 2012). The mean total score for males is 62.8 ($SD = 9.2$) and females 62.1 ($SD = 10.6$), and combined mean 62.3 ($SD = 10.3$) from an adult sample of $N = 1,577$ (m 393, f 1,184) where a score of 74 is generally considered to indicate impulsiveness as it is one standard deviation above the mean reported by Patton et al. (1995), although a score of 72 has been suggested as more appropriate (Coutlee et al., 2014; Stanford et al., 2009). Scores between 51-71 are generally considered to represent healthy levels of impulsivity while scores below 52 represent individuals who are over controlled or may have misreported the self-report measure (Stanford et al., 2009).

The BIS-11 scale is considered to have strong concurrent validity and has been the subject of many studies across a plurality of heterogeneous clinical and non-clinical populations (Stanford et al., 2009). Internal validity is considered strong as is test-retest reliability with Cronbach's alpha (internal consistency) at .83 (generally considered good) and test-retest correlation coefficient and Spearman's Rho (rank correlation) at .83 (Stanford et al., 2009; Vasconcelos et al., 2012). Of the three second order Factor II sub-traits above, motor impulsiveness has been shown to have the highest correlation with the go/no-go (GNG) and stop-signal tasks (SST) described below (Kam et al., 2012). Further, as noted above, the BIS-11 was

developed primarily and heavily used with college student populations and is deemed very valid for use in this population, a population included in the instant study (Kam et al., 2012).

Coding Changes to the BIS-11. Millisecond's implementation of the BIS-11 only reports the six Factor I subscale scores and not the three Factor II subscale scores. The IQML/IQScript computer source code (similar to HTML and JavaScript) was revised to add each pair of Factor I subscale scores to obtain Factor II subscale scores for each of motor (expressions.Motor_FII), attentional (expressions.Attention_FII), and non-planning (expressions.Non-Planning_FII) impulsivity. These new variables were then added to the 'summaryoutput' file leading with the motor impulsivity Factor II and Factor I subscales. The customized BIS-11 was then tested for six runs using dummy participants to confirm proper reporting of the above variables.

Wisconsin Card Sorting Test

The Wisconsin Card Sorting Test (WCST) was used in this study as both a proxy measurement of a neurobiological endophenotype comprising prefrontal cortical function and executive function (instrument shown in Appendix F). Permission to use the WCST for this study was provided by a license from Millisecond Software. The WCST (Grant & Berg, 1948; Heaton et al., 1993) is a laboratory behavioral measure that was developed to test complex cognitive functioning in subjects with neurofunctional impairment, namely brain lesions (Eling et al., 2008). The WCST was initially developed by Esther Berg in 1948 as a master's thesis, under the supervision of David Grant at the University of Wisconsin, to assess one's ability to apply and internalize a strategy to adapt behavioral responses to changing conditions, namely by set shifting (Eling et al., 2008). The WCST is now most notably used to evaluate impairment of the prefrontal cortex, more specifically, the dorsolateral prefrontal cortex (dlPFC), and basal

ganglia, the latter the origin (after receiving projections from the ventral tegmental area [VTA] of the midbrain) of key dopaminergic neural networks, namely the corticostriatal, mesolimbic, and nigrostriatal neural circuits, that project to the prefrontal cortex (PFC) and both regions implicate putative executive functions, including impulsivity and its subtypes (Gerfen & Bolam, 2010; Lange et al., 2018; Monchi et al., 2001; Puente, 1985). The WCST is also used to study inhibition specifically and has been used in concert with the go/no-go and stop-signal tasks, which have been suggested to be the best laboratory correlates to the WCST's inhibition related measures (Steinmetz & Houssemand, 2011).

The WCST can be administered using 128 response cards (split into two decks of 64), or their virtual equivalents via computer or on-line, with each card containing a triangle, circle, star, or plus sign displayed in yellow, red, blue, or green appearing on each card one to six times, and four so called stimulus cards (Puente, 1985). Participants are asked to arrange the cards according to object, color, or number of objects at each iteration guided by the stimulus cards and then given feedback as to whether they used the correct heuristic, using that feedback to identify the correct ruleset required to arrange the cards until they correctly arrange them a plurality of times, thus effecting some priming to the ruleset, which can lead to perseverative responses due to habitual loading or priming by multiple iterations of the prior ruleset (Monchi et al., 2001; Puente, 1985). The ruleset blindly changes sporadically with given iterations so participants must inform their ruleset with new feedback and so-called set shift (Monchi et al., 2001; Puente, 1985).

The WCST comprises six operational measures: correct responses, incorrect responses, preservative responses (PR; i.e., a response that would have been a correct response in the previous iteration), non-perseverative incorrect response (so called non-perseverative errors

[NPE]), and preservative incorrect responses (so called perseverative errors [PE], Puente, 1985). Additional operational measures include percent of preservative incorrect responses (percent perseverative errors), trials to complete first category, learning to learn (a measure of cognitive flexibility), and failure to maintain set (FMS; Puente, 1985).

To evaluate construct validity of the WCST, various studies have undertaken dimensionality reduction methods, including principal component analysis (PCA), exploratory factor analysis (EFA), and confirmatory factor analysis (CFA), to test and validate the WCST, with a loading of three factors most common (Greve et al., 1998; Greve et al., 2005). Factor I most significantly loaded preservative responses (PR), preservative incorrect responses (perseverative errors [PE]), correct responses, categories completed, and conceptual level responses; factor II most significantly loaded non-perseverative incorrect responses (non-perseverative errors [NPE]); and factor III most significantly loaded the failure to maintain set (FMS) measure and these loadings were stable across various clinical samples (Greve et al., 1998; Greve et al., 2005). Perseverative scores (responses) are most closely associated with neurobiological correlates, most notably the dorsolateral prefrontal cortex (dlPFC), while high failure to maintain set (FMS) measure most notably associated with the ventromedial (vmPFC) and orbitofrontal (OFC) prefrontal cortex and high non-perseverative incorrect responses (non-perseverative errors [NPE]) associated with aggressive impulsivity and inhibition (Greve et al., 2005; Steinmetz & Houssemand, 2011). However, a majority of studies support a neural network association for deficits in given measures rather than neuroanatomical or neurofunctional loci association (Nyhus & Barcelo, 2009). Further, numerous studies suggest that all 128 cards should be completed for all participants, and no stoppage at six categories completed (i.e.,

eliminating two discontinuation rule studies, as is common in many studies) to better capture Factors II and III, which were most relevant for this study (Greve et al., 2005).

Parameter Settings for the Wisconsin Card Sorting Test (WCST). Millisecond Software's implementation of the WCST has default parameter settings that are appropriate for this study. However, those default settings include stoppage at six categories completed, which is common in many studies. As discussed above, this rule is suboptimal for Factors II and III of the WCST, which were critical for this study. Consequently, these were manually altered in the source code for the WCST software to eliminate the six categories completed trigger, so all participants saw 128 cards. In order to force the WCST to run the full set of 128 cards, the value 'parameters.cstotalblocks' was set to an arbitrarily high value as follows: <parameters> [carriage return] /cstotaltrials = 128 [carriage return] /cstotalblocks = 10.

Coding Changes to the WCST. Millisecond Software's implementation of the WCST does not calculate or report non-perservative errors (NPE). Consequently, the IQML (similar to HTML) and IQScript (similar to JavaScript) code was revised to extract this variable. A new mathematical expression was created (expressions.number_npErrors) to subtract perservative errors from total errors (i.e., expressions.number_Errors - expressions.number_pErrors). The new NPE variable was then added to the summary output file reporting section for the source code. WCST was run under experimental conditions at least six times to test the accuracy of calculation and reporting of non-perservative errors (NPE) and verified using manual calculations.

Go/No-Go Task

The go/no-go (GNG) task was used in this study as a laboratory behavioral measure of prepotent response inhibition, Barkley's first facet of behavioral response inhibition (BRI).

Permission to use the GNG for this study was provided by a license from Millisecond Software (instrument shown in Appendix D). The origins of the GNG date back to 1869 in an article by Donders in German, translated into English one hundred years later (Donders, 1969). The GNG was developed as an alternative to a two-choice task to measure response times (RT) whereby the alternate choice must be inhibited (Donders, 1969; Gomez et al., 2007). Later, the GNG was applied to the lexical decision task by Gordon and Caramazza (1982). Many variants, versions, and implementations of the GNG have been developed in the literature. This study used a cued GNG developed by Fillmore et al. (2006).

The GNG task putatively measures behavioral response inhibition of a prepotent task (prepotent response inhibition) by requiring participants to respond quickly using a button to a series of frequent stimuli, such as letters, and requiring participants not to respond when the letter X, for example, appears infrequently and sporadically (DeYoung & Reuter, 2016; Michałowski et al., 2015). The go/no-go task can be administered in different forms, and measurements often include number of commission errors (CE; false go responses), number of omission errors (OE; false no-go responses), reaction time (often reported as mean reaction time [mRt]), and post error slowing of reaction time (conflict detection) measured as the difference between the mean reaction time after a false no-go response and the mean reaction time after correct no-go responses. In one study, for example, participants were asked to press the space bar on a computer when the letter 'A' appeared (the go signal) and to inhibit (not respond) to any occurrence of the letter 'P' (the no-go signal; Michałowski et al., 2015). There were 48 go and 16 no-go letters that appeared for 250 milliseconds in a random fashion separated by 3.5-4.5 second intervals (Michałowski et al., 2015).

The go/no-go task has been criticized for lack of convergent validity with great variety in types of stimuli (letters, colors, numbers, symbols) and measurement parameters including proportion of go and no-go signals, and time delay of signal and separation of stimuli (Langenecker et al., 2007). Consequently, validity and reliability measures generally depend on the particular version or iteration of the GNG. One study, for example, used a three level GNG termed a parametric go/no-go (PGNG) wherein the go signal shifts the no-go signal (set shifting) such that the letters, x, y, and z, in this case, were go triggers in a set of the entire alphabet appearing in random intervals separated by 500 milliseconds, followed by only x and y as go signals in another series, and in a third series the signals shift, showed strong convergent and test-retest reliability (Langenecker et al., 2007).

Parameter Settings of the Go/No-Go Task (GNG). To operationalize parameter settings of the GNG with the implementation of the GNG by Millisecond Software (Versions 6.6.1, 6.6.2, and 6.6.3 of Inquisit Lab), a key literature review by Wessel (2017) was considered. Wessel (2017) analyzed various implementations of the GNG and identified certain parameter settings that maximize the GNG task construct and convergent validity. Wessel (2017) identified the following optimal parameter settings: probability of no-go (pNoGo) of .2, probability of go (pGo) of .8, trial duration of 1,500 milliseconds, use of a + fixation cross in between stimuli, a response timeout of 1,000 milliseconds, and 250 total trials. These settings were used as a starting point for the implementation of the GNG task for this study from Millisecond Software. The default settings in Millisecond's implementation are different. However, they were altered manually using Millisecond's programming language (IQML and IQScript, which are similar to HTML and JavaScript, respectively) in the source code itself. For example, Wessel (2017) suggestion for no-go probability was set by altering a line of code as follows: <block testblock>

/trials = [1-250noreplace (4:1 ratio of vertical go to vertical no-go and 4:1 ratio of horizontal go to horizontal no go)] where each cue in the parenthetical is repeated four times for *go* and once for *no-go*, for each of horizontal and vertical cues. The ‘/pool size’ fields in the source code were similarly changed to 100 for go trials and 25 for no-go trials for each of horizontal and vertical cues (green or blue rectangles) for 250 trials total. Consequently, the final parameters manually included the following after various optimization trials using the software: fixation duration (+) of 400 milliseconds, cue delay (+ to white rectangle cue) of 200 milliseconds; response timeout (time to respond post cue) of 1,000 milliseconds, intertrial interval (iti) of 500 milliseconds, and 250 trials (including 50 no-go trials). The above followed the assumption that response timeout + intertrial interval = trial duration of 1,500 milliseconds to match Wessel (2017). In addition, data was excluded if there was evidence of low task effort as reflected in commission error (CE) rate of greater than .8 or omission error (OE) rate of greater than .5 as described in Deng et al. (2023).

Coding Changes for the Go/No-Go Task (GNG). Millisecond Software’s implementation of the GNG task reports commission and omission errors as rates, which is common in the literature. However, use of absolute error counts provides several methodological advantages. First, use of rates can compress information in the data, making it more difficult to statistically resolve differences. Second, use of absolute error counts improves resolutional precision in the data, which is important for feature selection for AI models, which work better with raw counts versus rate-based features. Third, use of absolute errors increases sensitivity in that differences between groups are compressed when rates are used. Fourth, rate compression masks outliers where use of absolute error counts makes extreme influential outliers (e.g., via Cook’s sensitivity analysis) more apparent, which improves model robustness. Fifth, use of

absolute error counts is arguably more appropriate for MANOVA analysis in that there would be greater variance in the data due to lack of rate compression, data distributions are more calculable and predictable, and effect size detection would improve versus rates. Sixth, rates are agnostic to trial numbers and test blocks, which mask differences in performance levels between studies in the literature, particularly where disparate measures are used (e.g., GNG vs. SST) making cross-measure comparisons difficult to interpret.

Finally, arguably, the literature places too much reliance on measures of test-retest reliability (typically appropriate for trait measures) versus internal consistency validity measures for state based laboratory behavioral tasks. Internal consistency measures are arguably more meaningful for state measures (Green et al, 2016; Tavakol & Dennick, 2011; Sutherland et al, 2024). Rates do not lend themselves to internal consistency measures because they are agnostic to trial or block numbers and thus artificially compress variance. Absolute error counts enable calculation of internal consistency which can provide more meaningful instrument validity data (Green et al., 2016; Tavakol & Dennick, 2011; Sutherland et al, 2024). For example, trial-by-trial performance in a laboratory behavioral task measure, such as the SST, arguably practically equates to items in a self-report scale. Consequently, internal consistency, including Cronbach's alpha, can be calculated for the instruments used in this study, since absolute error counts and trial numbers were collected and reported, providing valuable information typically absent in the literature of such instruments (Green et al, 2016; Tavakol & Dennick, 2011; Sutherland et al, 2024).

Consequently, in light of the above, the IQML/IQScript (similar to HTML and JavaScript) computer source code was revised to report the absolute number of commission errors (`expressions.commission_errors`) and omission errors (`expressions.omission_errors`) by

multiplying the rates (`expressions.commission` and `expressions.omissionrate`) by the number of no-go (stop) trials (here 50, using `list.soa_verticalcue_nogo + list.soa_horizontalcue_nogo.poolsize`) and the number of go trials (here 200, using `(list.soa_horizontalcue_go.poolsize + list.soa_verticalcue_go.poolsize)`), respectively. These new variables (`expressions`) were then added to the ‘summarydata’ output sections to be reported first along with mRt (note that rates were still collected for comparison and reanalysis purposes). The go/no-go custom code was tested using dummy participants for at least six runs to confirm accurate calculation and reporting of the above variables.

Stop-Signal Task

The stop-signal task (SST; Lappin & Eriksen, 1966; Logan, 1994; Logan & Cowan, 1984; Vince, 1948) was used in this study as a laboratory behavioral measure of prepotent response extinction, Barkley’s second facet of behavioral response inhibition (BRI). Permission to use the SST for this study was provided by a license from Millisecond Software (instrument shown in Appendix E). The SST originated with the work of Logan and Cowan (1984) who developed a stop-signal procedure in combination with a theory regarding the stop-signal paradigm. The SST is based on an independent race model (Logan & Cowan, 1984; Senkowski et al., 2023; Verbruggen et al., 2019). The first runner (the go runner) is initiated by a go stimulus (Verbruggen et al., 2019). The second runner (the stop runner) is triggered by a stop stimulus initiated after the go stimulus (Verbruggen et al., 2019). In the SST, inhibition is a latent hidden dependent variable, since successful inhibition cannot be observed (Verbruggen et al., 2019). When the stop runner responds to the stop stimulus after a response latency (stop signal reaction time [SSRT]) before the go runner finishes its response to the go stimulus (response latency to a go stimulus measured in reaction time [RT]) the go response is successfully inhibited

(Verbruggen et al., 2019). The race is won by successful inhibition if the stop response latency is shorter and finishes earlier than the go response latency (Verbruggen, 2019).

Applying the independent race model, the SST measures inhibition (interruption or extinction) of an ongoing response (termed for this study as prepotent response extinction) by adding to a go/no-go task a stop task after the go signal is given, to inhibit the go signal 25% of the time with successful responses, increasing difficulty (delayed interval) in subsequent trials, and unsuccessful responses followed by decreasing difficulty so as to conclude the test where the subject inhibits roughly 50% of the go trials (signals; a forced regression toward the mean often referred to as the staircase algorithm; Michałowski et al., 2015; Logan, 1994; Senkowski et al., 2023; Verbruggen & Logan, 2008). The measurement for the stop-signal task covert latency is the stop-signal reaction time (SSRT) with a slower (longer) SSRT indicating impulsivity (disinhibition), thus making the SSRT a clinical marker of behavioral response inhibition (Eagle et al., 2008; Michałowski et al., 2015; Logan, 1994; Verbruggen et al., 2019; Verbruggen & Logan, 2008). In the SST, the go signal is often either an ‘O’ or an ‘X’ or (as in the Millisecond Inquisit 6 implementation used for this study) a right arrow (→) or left arrow (←) with a response with a right hand (on the letter ‘k,’ for example) for one and left hand (on the letter ‘d,’ for example) for the other with the stop signal often presented as an auditory tone, with a stop signal time delay (SSD), following the go signal, invoking a cancellation or withdrawal (inhibition or extinction) process (Soreni et al., 2009).

The SST is considered a putative endophenotype for DSM behavioral phenotypes (mental disorders) that implicates the dorsolateral prefrontal cortex (dlPFC), pre-supplementary motor area (preSMA), right inferior frontal cortex (rIFC), subthalamic nucleus (STN), and striatum (STN) incorporating frontostriatal neural circuits (Aron, 2011; Aron et al., 2014). It has been

used with both neurotypical populations and a plurality of behavioral phenotypes including ADHD, ASD, and schizophrenia (Lipszyc & Schachar, 2010). Interestingly, the SST has shown more significant deficits in SSRT for obsessive compulsive disorder (OCD) than for ADHD, ASD, or schizophrenia (Lipszyc & Schachar, 2010) perhaps suggesting its role as a potential measure of latent compulsivity and preservation (see discussion on impulsivity versus compulsivity in Chapter 2).

The SST has been found to have strong discriminant validity, for example, in ADHD children, as well as strong test-retest reliability (SSRT ICC = 0.72; Soreni et al., 2009). However, like with the GNG task, the SST's construct and convergent validity has been called into question due to considerable heterogeneity in its design, parameter settings, implementation, estimation of measures, and reporting of results (Senkowski et al., 2023; Thungberg et al., 2024; Verbruggen et al., 2019). To maximize construct and convergent validity, this study used an implementation of the SST that attempted to optimize the criteria set forth in Senkowski et al., (2023) and Verbruggen et al. (2019), including two-choice reaction (discrimination) tasks using left ($\leftarrow$) and right ($\rightarrow$) keyboard arrows, use of a salient auditory stop signal at an optimal volume, use of a 25% stop-signal frequency, 50 or more stop signals, response sensitive variation in stop signal delay (SSD) increasing with successful trials and decreasing with unsuccessful trials (i.e., the staircase algorithm), probabilistic convergence on 50% successful inhibition, participant tracking, practice blocks, fulsome and repeat instructions, statistically significant number of trials, fulsome reporting to test for assumptions, and cut-offs (data rejection filters) to ensure valid SSRT values and filter failed race model assumptions a stop accuracy range of 25%-75% per Arnatkeviciute et al. (2023) and exclusion of illogical task completion times (times

exceed maximum possible sum of all task runs with no response or values are less than or greater than five standard deviations from the mean).

Further, the SSRT is often estimated using two non-parametric methods, the integration method, which calculates the RT distribution at the point where its integral equals the probability of response to the signal, and the mean method, which uses the mean of the inhibition function of the probability of response to the signal and the SSD (Verbruggen et al., 2019). Based on various analysis, although the mean method is simpler and the most common method used in the literature, the integral method is arguably a better non-parametric estimation method of the SSRT (Senkowski et al., 2023; Verbruggen et al., 2013; Verbruggen et al., 2019). The SST implementation by Millisecond Software used the settings in Verbruggen et al. (2019) and the SSRT value used the integration method for this study, although it also calculated SSRT using the mean method for comparison.

Parameter Settings of the Stop-Signal Task (SST). Consistent with operationalizing the previous paragraph with respect to optimizing parameter settings of the SST, the following parameter settings were used for Millisecond Software's version of the SST implementation for this study: minimum SSD: 50 milliseconds; maximum SSD: 1150 milliseconds; adjustment: 50 milliseconds; SSD start: 250 milliseconds; pretrial pause: 500 milliseconds; trial duration: 2000 milliseconds; wait between blocks: 10 seconds; $P = 0.5$. In addition, in response to optimization in the previous paragraph, the implementation of the SST used an audible tone with instructions on setting the sound to a consistent level.

Coding Changes for the Stop-Signal Task (SST). For this study, the IQML (similar to HTML) and IQScript (similar to JavaScript) source code was revised to extract two of the three dependent variables for this study: commission errors (CE) and omission errors (OE). The

Millisecond Software implementation of the SST (Millisecond Lab versions 6.6.1, 6.6.2, and 6.6.3 for Windows) for this study contains one practice block and three test blocks (of 72 trials each for 216 total trials per experiment/participant). Millisecond Software's implementation of the SST does not measure the total of these measures across test blocks (only within test blocks) and does not report any of these variables (they are arguably treated as latent variables) to data or summary output files. Both commission errors and omission errors were reported as absolute error counts across all blocks rather than blockwise as rates for the same reasons discussed in the previous section for the GNG model, although rates were still collected for future reanalysis or comparison.

Commission errors (CE) were calculated within practice and test blocks (blockwise) through the value 'ss_nresp', which means a participant has responded to the go signal even after a stop (stop trial) command (i.e., the participant responded incorrectly to a stop command by failing to extinguish the go response). SQML/SQScript is an object-based programming environment. The value for the commission error (value.ss_nresp) for a given trial (iteration) was set = '0' on initialization of an experiment. The Millisecond IQML/SQScript object (code section) for the stop-signal trial collects 'ss_nresp' at the end of the trial (via the 'ontrialend' element) using a conditional 'else' statement, incrementing it (blockwise) from the prior 'ss_nresp' value by '1.' At the beginning of each block, it resets 'value.ss_nresp' from the prior block to '0' in the 'onblockbegin' element. Thus, this variable only represents blockwise commission errors and not total commission errors for the SST experiment (across three test blocks in the current study).

For this study, a new variable (value.t_commission_errors) was added to the values section and also initialized to equal '0.' Then, additional IQScript code was added to the same

conditional ‘else’ statement in the stop-signal trial (object element) to record and increment the same measure as ‘value.ss_nresp.’ Thus, the only difference between ‘value.ss_nresp’ and ‘value.t_commission_errors’ is that the latter is not reset to zero at the beginning of the block. Consequently, ‘value.t_commission_errors’ represents the aggregate commission errors across all three test blocks. To ensure that the total commission errors exclude commission errors from the practice block, an additional conditional ‘if’ Boolean statement was added as a condition precedent to the iteration of ‘value.t_commission_errors’ where this variable was incremented only if ‘value.blocknumber’ did not equal ‘PRACTICE’ (using the ‘!=’ comparison operator). The new variable (value.t_commission_errors) was then reported to the data files in the ‘data’ element (trial by trial along with ‘value.ss_nresp’) and to the ‘summarydata’ element (experiment/participant by experiment/participant).

Omission errors (OE) were calculated within practice and test blocks (blockwise) through the value ‘ns_nnoresp’, which means a participant has failed to respond to the go signal even though there was no stop (stop trial) command (i.e., the participant omitted a go response when it was warranted to press a go response). All the same corresponding code revisions above (as done for commission errors) were made to extract omission errors using a new variable (value.t_omission_errors) in the ‘no-signal’ trial object source code. All code was tested under experimental conditions and tested with forced dummy fixed responses on certain trial intervals for at least six runs to confirm accurate calculation and reporting of the above variables.

Operational Definitions of Variables

Table 9 lists variables for each of the three studies by research question (RQ) and by both type of variable (independent vs. dependent) and type of data (dichotomous, interval [discrete, continuous]) that comprises the variable. For each study, the independent predictor variable (IV)

is dichotomous (two factor levels) comprising high and low trait motor impulsiveness subscale on the Barratt Impulsiveness Scale (BIS-11) self-report measure. Each study contains three dependent response (outcome) variables that were selected subscales of each of the three laboratory behavioral instruments (Wisconsin card sorting test [WCST], go/no go task [GNG], and the stop-signal task [SST]).

Table 9

Types of Variables Used in This Study

RQ/Study	Variables	IV/DV	Data Type
1			
BIS-11	Factor I Motor Impulsiveness (FI- MI)	IV	Dichotomous
WCST	Perseverative responses (PR)	DV	Interval/Discrete
	Non-perseverative errors (NPE)	DV	Interval/Discrete
	Failure to Maintain Set (FMS)	DV	Interval/Discrete
2			
BIS-11	Factor I Motor Impulsiveness (FI-MI)	IV	Dichotomous
GNG	Mean reaction time (mRt)	DV	Interval/Continuous
	Commission errors (CE)	DV	Interval/Discrete
	Omission errors (OE)	DV	Interval/Discrete
3			
BIS-11	Factor I Motor Impulsiveness (FI-MI)	IV	Dichotomous
SST	Stop Signal Reaction Time (SSRT)	DV	Interval/Continuous
	Commission errors (CE)	DV	Interval/Discrete
	Omission errors (OE)	DV	Interval/Discrete

Note: IV = independent variable; DV = dependent variable.

Construct 1: Impulsivity

The construct of impulsivity was operationalized into a measurable independent variable of trait motor impulsiveness via a self-report measure using the most widely used and validated psychometric self-report instrument to measure trait impulsivity, the Barratt Impulsiveness Scale version 11 (BIS-11). The BIS-11 comprises 30 questions that measure six impulsivity first order factors: attentional impulsiveness, motor impulsiveness, self-control, cognitive complexity, perseverance, and cognitive instability; that comprise three second order factors (subtraits): non-planning impulsiveness (lack of premeditation or precognition), motor impulsiveness (action without thought), and attentional impulsiveness (the inability to concentrate; Coutlee et al., 2014; Patton et al., 1995; Stanford et al., 1999). BIS-11 high and low Factor I trait motor impulsivity scores comprised dichotomous independent variables (Table 9) to establish control and treatment groups for the study for each primary research question.

Variables 1-3: Behavioral Response Inhibition, Prepotent Response Inhibition, and Prepotent Response Extinction

Operationally, behavioral response inhibition (BRI), or lack thereof (disinhibition), is a measurable facet of impulsivity and is commonly measured in the laboratory (rather than via a self-report measure) through a plurality of dependent variables (Table 9). The first facet of Barkley's classification of behavioral response inhibition, prepotent response inhibition, was measured by three dependent variables comprising scales of the go/no-go task (Table 9; DeYoung & Reuter, 2016; Dougherty et al., 2005). The second facet of Barkley's classification of behavioral response inhibition, prepotent response extinction (inhibition of an ongoing

response that has already started), was measured by three dependent variables comprising scales of the stop-signal task (Table 9; DeYoung & Reuter, 2016; Dougherty et al., 2005). The third facet of Barkley's classification of behavioral response inhibition, interference control, is often measured by the flanker task or the Stroop test, which measure of the ability to filter out extraneous stimuli (Tillman & Wiens, 2011). Each facet of behavioral response inhibition was treated as a subtype of behavioral response inhibition, and thus impulsivity, and, consequently, as a potential differentiable endophenotype, with prepotent response inhibition and prepotent response extinction being the particular focus of study here and not interference control.

Study Procedures

This study utilized a Qualtrics research panel to recruit study participants using non-probability convenience sampling after certain inclusion and exclusion criteria were met. The study design used the BIS-11 as a pre-test condition and dichotomous control and experimental treatment grouping and a battery of three laboratory behavioral measures. Data was collected using a Qualtrics gateway with a JavaScript portal to link Qualtrics with on-line versions of the instruments through the Inquisit 6 Web data software package from Millisecond Software (using query parameter 'subjectID' handoffs from Qualtrics JavaScript to Millisecond IQScript). Statistical analysis included MANOVA for primary effects (for each of three main research questions) and post hoc independent samples *t*-tests (or Welch's *t*-test) to identify which dependent variables were the primary sources of differences between groups for each laboratory behavioral measure, Cook's leverage-residual (influence) sensitivity analysis to improve statistical power, and cross-model convergent analysis to identify frameworks of linear variates that demonstrated optimal power-parsimony.

Data Collection and Sampling Procedures

Initially, volunteer male participants 18-34, and after pilot testing, male and female participants 18-40, were recruited through Qualtrics via access to its research panel of participants. Panel members were existing and pre-selected, qualified, and screened by Qualtrics and then existing members were given the option to opt-in to a given study after notice of the study from Qualtrics. Remuneration was offered by Qualtrics to aid in enrollment, interest, and completion under its standard research panel contract with participants. As a back-up, only if needed, participants may have been recruited from three local college campus sites (University of California, San Diego; San Diego State University, and Miracosta Community College). The choice of three college campuses of different types and standing was intended to ensure that a broader demographic is captured and to facilitate cluster sampling to ensure ethnic diversity. With respect to back-up sampling, after institutional IRB permissions would have been obtained, notices would have been posted on campus bulletin boards, social media groups, and through psychology programs. Interested participants would then be able to call or email the provided contact.

Inclusion/Exclusion Criteria. Interested participants were asked seven preliminary questions as follows: age 18-34 (through pilot testing)/18-40 (yes, no), , biological gender of male at birth (yes, no; through pilot testing); right handedness (yes, no), normal hearing ability without use of hearing aid (yes, no), normal vision with or without corrective lenses (yes, no), color blindness (yes, no), English proficiency seventh grade or higher (yes, no). Any participants who answered no to any of the seven preliminary questions were excluded from this study and directed to an exit screen. The remaining participants completed informed consent over a Qualtrics on-line gateway using an IRB form approved by both Qualtrics and the NCU IRB.

Informed consent included a disclosure that the identity of each participant would be deidentified by Qualtrics and neither visible to the researcher nor linked with any individual questionnaire or results or confidential information associated with such participant. A unique numerical identifier (subjectID) that was not linked to any personal identifying information was assigned by Qualtrics for each participant that was then ported to the Millisecond Software portal and back again using JavaScript and IQScript batch scripts.

After participants completed informed consent, they were asked two sets of additional screening questions. The first set of three questions related to additional demographic information that may be useful for future analysis or future reanalysis, including meta-analysis: race (white/Caucasian, black/African American, native American, Asian, pacific islander, mixed, prefer not to answer), ethnicity (Hispanic/Latino, non-Hispanic/Latino, mixed, prefer not to answer), and education level (less than high school, some high school, high school, some college, college, masters, doctorate, prefer not to answer).

The second set of two questions were asked to help identify possible confounding variables for future analysis, reanalysis, or meta-analysis. A preface to the questions explained to participants that the questions were being asked solely to help identify items that may help explain or influence results. First, each participant was asked (they could opt not to answer) whether they have (or previously had) a DSM (or DSM related) formal clinical diagnosis, particularly an externalizing disorder that implicates impulsivity and or dopaminergic systems (mesocortical, mesolimbic, nigrostriatal), including ADHD, ASD, schizophrenia, schizoaffective disorder, schizophreniform disorder, schizotypal personality disorder, borderline personality disorder, narcissistic personality disorder, histrionic personality disorder, antisocial personality disorder, self-disorder, conduct disorder, oppositional defiant disorder, reactive attachment

disorder, intermittent explosive disorder, bipolar disorder, substance use disorder (drug or alcohol addiction), gambling disorder, disruptive or impulse control disorder, including pyromania and kleptomania; paraphilic disorder, PTSD, obsessive-compulsive disorder or obsessive compulsive personality disorder, anxiety disorders, Tourett's disorder, adjustment disorder, and other psychiatric diagnosis or Parkinson's Disease. Next, each participant was asked (they could opt not to answer) whether they were taking any of the following medications at the time of testing (within the last 24 hrs) that implicate impulsivity and dopaminergic systems: methylphenidate, amphetamine salts, Adderall, Ritalin, Concerta, Dexedrine, Vyvanse, Focalin, Strattera (atomoxetine), Intuniv, Wellbutrin (bupropion), Provigil (modafinil), or any beta-blockers, including, Lopresor (metoprolol), Betaloc (metoprolol), Inderal (propranolol), carvedilol, Nebilet (nebivolol), Bystolic (nebivolol), Corgard (nadolol), Zebeta (bisoprolol), Cardicor (bisoprolol), Emcor (bisoprolol), Tenormin (atenolol), Secretal (acebutolol), or unprescribed street drugs (amphetamine, cocaine, MDMA [Molly, Ecstasy], cannabis [marijuana]).

Participants were excluded who did not complete the BIS-11 and all laboratory behavioral measures. Scores were analyzed for outliers, including use of Box plots and *z*-score analysis (Mahalanobis distance and Cook's distance), particularly for participants who scored 51 or lower on the BIS-11 total score, because such scores may indicate misreporting (Stanford et al., 2009). Conservatively, confirmed outliers were excluded from the results for sensitivity analysis only to ensure robustness of the models.

Study Design

Each participant was subject to the following battery of tests:

Pre-test condition: BIS-11 Self-report measure of trait motor impulsivity (an independent predictor variable).

Control Group: BIS-11 Total and Factor I and Factor II subscale motor impulsiveness score for those participants who scored in the bottom quartile.

Experimental Group: BIS-11 Total and Factor I and Factor II subscale motor impulsiveness who scored in the top quartile.

Model 1. Laboratory behavioral assessment (treatment with observation) to measure neurobiological correlates associated with behavioral response inhibition using the Wisconsin Card Sorting test (WCST)

Model 2. Laboratory behavioral assessment (treatment with observation) to measure neuropsychological correlates associated with behavioral response inhibition using the go/no-go task (GNG).

Model 3. Laboratory behavioral assessment (treatment with observation) to measure neuropsychological correlates associated with behavioral response inhibition using the stop-signal task (SST).

Behavioral measure outputs were generally consistent with instrumental standards, except as indicated above for dependent variable extraction (Braunstein, 2014; Markovska-Simoska & Pop-Jordanova, 2017; Nash et al., 2013; Shahaf & Pratt, 2013; Tye et al., 2011).

Data Collection Procedures

All data collection utilized the Inquisit 6 Web data collection suite software licensed from Millisecond Software (Seattle, Washington) via Qualtrics on-line using a unique link to a

JavaScript and IQScript enabled gateway after verification of informed consent and completion of all screening questions. As a back-up, access may have been provided via the Inquisit 6 Web data collection suite directly to Millisecond Software. In both cases, participants would be able to complete all instruments on-line. Both Qualtrics and Millisecond have a rigorous set of data collection, presentation, confidentiality, security, and storage protocols.

Data collection occurred for the self-report measure of trait motor impulsivity, the BIS-11, and go/no-go (GNG) task, stop-signal task (SST), and Wisconsin card sorting test (WCST) laboratory behavioral measures. The screening questionnaire, informed consent, additional screening questions, self-report measure, and all laboratory behavioral measures could be completed in under one hour. Once participants completed the BIS-11 self-report measure, presentation of each of the remaining three laboratory behavioral measures was randomized. This addressed risks of temporal familiarity and order of completion bias from one related laboratory behavioral measure (instrument) to another.

BIS-11 Self-Assessment Questionnaire. Participants were administered the BIS-11 self-assessment questionnaire via the Qualtrics gateway to the Millisecond portal. The format was that of a 30 question Likert scale using click dots. All inputs were deidentified after informed consent. BIS-11 total scores and Factor I and Factor II motor impulsivity subscale scores were collected for each participant in addition to other measures not used in this study.

Wisconsin Card Sorting Test. Participants were administered the Wisconsin card sorting test (WCST) via a Qualtrics gateway to the Millisecond portal on-line using a unique link after verification of informed consent. Perseverative responses (PR) were collected for each participant as well as non-perseverative errors (NPE) and failure to maintain set (FMS) and other measures that were not included in this study.

Go-no go Task. Participants were administered the go/no-go (GNG) task via a Qualtrics gateway to the Millisecond portal on-line using a unique link after verification of informed consent. Mean reaction time (mRt) was collected for each participant as well as the number of commission errors (CE) and number of omission errors (OE) and other measures that were not included in this study.

Stop-Signal Task. Participants were administered the stop-signal task (SST) via a Qualtrics gateway to the Millisecond portal on-line using a unique link after verification of informed consent. Stop signal reaction time (SSRT) was collected for each participant, as well as the number of commission errors (CE) and number of omission errors (OE) and other measures that were not included in the study.

Pilot-Testing. Prior to full launch of this study for data collection, preliminary pilot testing (under experimental conditions with dummy participants) was conducted to test the operation and function of the survey (gateways, screening questions, informed consent, software to host questions and testing and link to external web hosts, links to instrument software portals, instrument software and parameter settings, coding, instrument operation, and data collection and reporting), including confirmation of proper parameter settings for all instruments and accurate calculation and reporting of each dependent variable.

For full pilot testing, Qualtrics uses a protocol it terms *soft launch* to field test surveys on 10% of the target sample, so approximately 60 participants for this study (Qualtrics technical support, personal communication, May 17, 2023). For this study, the soft launch also helped provide a time estimate for full saturation of the participant pool. Consequently, instead of full pilot testing of 60 participants (10% of the target sample assuming 100% yield), due to a low number of completed studies, pilot testing continued until 580 participants attempted the study

(8% of the projected sample based on an 8% observed yield) after about 60 days of data collection. Following pilot testing, the sample pool was expanded to 18-40 year old males and females after IRB approval to improve yield (which increased to 13.8% following this change). Any results that were obtained from full pilot testing (soft launch), after correction of any issues or adjustments or changes needed to otherwise optimize and finalize the survey, were included in the final results data pool.

Data Analysis

Certain scale and subscale scores were collected for each instrument. For the BIS-11 instrument, top and bottom quartile Factor I subscale scores were calculated to determine the dichotomous independent predictor variable groupings (factor levels). Statistical analysis of dependent outcome variables included MANOVA with post hoc independent samples *t*-tests (or Welch's *t*-test) as described in detail below.

BIS-11 scores

BIS-11 total scores were tracked (range 30-120) and motor impulsiveness Factor I (range 8-28) and Factor II (range 11-44) subscale scores for each participant and means and standard deviations for the study sample. A cut off for BIS-11 total score is putatively 72 to indicate highly impulsive individuals (74 approximates one standard deviation above the mean for males) although a lower score of 69 was appropriate to allow for error and subsequent imputed regression towards the mean and demarcation of the upper quartile (see below). In this study, BIS-11 Factor II subscales for non-planning impulsiveness (NPI, range 11-44), attentional impulsiveness (AI, range 8-32), and motor impulsiveness (MI, range 11-44), as well as Factor I subscales for motor impulsiveness (range 7-28), were measured and reported per participant (case) and, min, max, and means and standard deviations.

As noted above, however, motor impulsiveness (via Factor I and Factor II subscale scores) has been shown to correlate most strongly with laboratory behavioral measures of behavioral response inhibition (Kam et al., 2012). However, no cut-offs have been established for the subscales (M. S. Stanford, personal communication, August 16, 2018). Consequently, the top and bottom quartile Factor I motor impulsiveness subscale scores were used for this study to demark high motor impulsiveness and low motor impulsiveness groups. Using the sample normed by Stanford et al. (2009) for males, z-scores, and the assumption that the lower and upper quartiles of a normal distribution are two thirds of a standard deviation from the mean, this would suggest total BIS-11 scores to be 57 or below for the lower quartile, 69 or above for the upper quartile, and Factor I motor impulsiveness scores (range 7-28) of 13 or below for the lower quartile or 17 or above for the upper quartile (assuming a theoretical baseline mean of 15 with a standard deviation of 3), and Factor II motor impulsiveness scores (range 11-44) of 20 or below for the lower quartile or 25 or above for the upper quartile (assuming a theoretical baseline mean of 22.5 and standard deviation of 3.7), although actual quartiles from the study sample were be used for this study as described in Chapter 4.

Wisconsin Card Sorting Test (WCST) perseverative responses, non-perseverative errors, and failure to maintain set

Perseverative responses (PR), non-perseverative errors (NPE), and failure to maintain set (FMS) for the Wisconsin card sorting test (WCST) were reported individually and min, max, means, and standard deviations.

Go/no-go task mean reaction time (mRT), Commission Errors and Omission Errors

Mean reaction times (mRt), commission errors (CE), and omission errors (OE) for go/no-go (GNG) task were reported individually and min, max, means, and standard deviations.

Stop-Signal Task stop-signal reaction time (SSRT), commission errors, and omission errors

Stop signal reaction time (SSRT), commission errors (CE), and omission errors (OE) for the stop-signal task (SST) were reported individually and min, max, means, and standard deviations.

Statistical Analysis

Table 10 shows the statistical analysis that was performed for each research question. IBM SPSS (Statistical Products and Service Solutions) Statistics 29 (April 2024 release) and 30 (September 2024 release) GradPack Java enabled software (International Business Machines Corporation [IBM]) for 64 bit Microsoft Windows was used for all statistical analysis. SPSS uses a 4GL command syntax language with macro enabled subroutine editing capability and Python extension optionality (for AI machine learning applications) that can also enable R statistical programming language bridging (IBM, 2023). SPSS can take data input from ASCII, spreadsheet, and database data structures, and SPSS .spv output data files can be exported to various file formats (IBM, 2023). SPSS was used for all assumption testing, outlier analysis, descriptive statistics, MANOVAs, and post-hoc independent samples *t*-test analysis and Welch's *t*-test (Table 10).

Following, the main analysis and, as appropriate, post hoc analysis, for all three behavioral models (WCST, GNG, SST), SPSS was also used for a Cook's leverage-residual (influence) sensitivity analysis and cross-model convergent analysis described below to interrogate model robustness, expandability, and to explain the connection between empirical results and theoretical framework so as to enable interpretation of findings in Chapter 5. The experimental design comprised a post-hoc pre-test design with one exogenous independent dichotomous predictor variable of BIS-11 trait motor Factor I impulsiveness score, and nine

endogenous dependent outcome variables of three laboratory behavioral measures (features: PR, NPE, FMS, mRT, CE, OE, SSRT, CE, OE) split into three studies (models; research questions) of each of the Wisconsin card sorting test (WCST), the go/no-go (GNG) task, and the stop-signal task (SST), of three dependent outcome variables each (one sub-research question for post hoc analysis of each dependent outcome variable for each laboratory behavioral measure). The types of variables in this study are shown above in Table 9.

Table 10

Summary of Statistical Analysis

Research Question	Type of Analysis	Descriptive Stats	Hypothesis Testing	Post-hoc Analysis
1				
BIS-11 + WCST	One-way One-factor (unpaired) MANOVA	Means, standard deviations, min, max, frequency for BIS-11 total, and motor impulsiveness Factor I and Factor II subscale scores, and PR, NPE, FMS for WCST	$p < .05$	Independent samples <i>t</i> -test (unpaired)
2				
BIS-11 + GNG	One-way One-factor (unpaired) MANOVA	Means, standard deviations, min, max, frequency for BIS-11 total, and motor impulsiveness Factor I and Factor II subscale scores and mRT, CE, and OE for go/no-go	$p < .05$	Independent samples <i>t</i> -test (unpaired)

Research Question	Type of Analysis	Descriptive Stats	Hypothesis Testing	Post-hoc Analysis
3				
BIS-11 + SST	One-way (unpaired)	Means, standard deviations, min, max, frequency for BIS-11 total, and motor impulsiveness Factor I and MANOVA Factor II subscale scores and SSRT, CE, and OE for SST.	$p < .05$	Independent samples <i>t</i> -test (unpaired)

MANOVA Analysis. One-way (one-factor) between subjects unpaired multivariate analysis of variance (MANOVA) was used to analyze the data from this study, because there was one independent grouping variable (a two-level factor) and multiple dependent outcome variables for each instrument, and a comparison of latent linear variates of composite means of the dependent outcome variables (Field, 2013; Huberty & Olejnik, 2006; Meyers et al., 2017; Tabachnick & Fidell, 2013). Although analysis of variance (ANOVA) cannot be performed with multiple dependent variables, it can be performed on each individual dependent variable (Field, 2013; Huberty & Olejnik, 2006; Meyers et al., 2017; Tabachnick & Fidell, 2013). Consequently, another analytical option was running multiple ANOVAs on the dependent outcome variables. While use of multiple ANOVAs was considered and is not uncommon in the literature, conducting ANOVA on each dependent variable was not appropriate for this study because conducting multiple analysis on the same data amplifies Type I errors (false positives; Field, 2013; Huberty & Olejnik, 2006; Meyers et al., 2017; Tabachnick & Fidell, 2013). Further, any

relationships between dependent variables are ignored in ANOVA (Field, 2013; Huberty & Olejnik, 2006; Meyers et al., 2017; Tabachnick & Fidell, 2013).

Unlike ANOVA, MANOVA can also detect differences between groups along a plurality of dimensions, in this case, along various combinations of instrumental subscales or facets (endophenotypes; Field, 2013; Huberty & Olejnik, 2006; Meyers et al., 2017; Tabachnick & Fidell, 2013). MANOVA also improves power and effect size by taking into account cross correlations between dependent outcome variables (Field, 2013; Huberty & Olejnik, 2006; Meyers et al., 2017; Tabachnick & Fidell, 2013). In addition, ANOVA tests differences among groups on variables that are observed, whereas MANOVA tests differences in latent variables (Meyers et al., 2017; Warne, 2014). The constructs of impulsivity and behavioral response inhibition and their facets are, after all, latent variables.

MANOVA also lends itself well to the use of multiple dependent outcome variables. The choice of several dependent outcome variables increases the chance of identifying the dependent outcome variable most significantly predicted by the factor level of group membership (control low motor trait impulsivity or treatment high motor trait impulsivity; Huberty & Olejnik, 2006; Meyers et al., 2017; Tabachnick & Fidell, 2013). Put differently, the process of decomposing state motor impulsivity (a top level endophenotype) into discriminate simultaneously measurable facets of two latent variables (facets) of behavioral response inhibition and prefrontal correlates (lower level decomposed [deep] endophenotypes) increases the chances of identifying which facets, factors, features, or components most strongly associate (correlational or orthologous) with high and low trait motor impulsivity differentially across the two latent variables (facets) of behavioral response inhibition and a measure of neurobiological correlates.

In the case of this study, each laboratory behavioral measure comprised a two-class vector matrix (participants and observations) with three observations (dependent outcome variables) per participant. MANOVA enabled the determination of how much variance (ratio of systematic [between groups] to unsystematic [within groups] residual variance cross-product correlation matrix) in each dependent variable on the matrix was accounted for by the dichotomous BIS-11 independent predictor variable groupings (factor levels; Field, 2013; Huberty & Olejnik, 2006; Meyers et al., 2017; Tabachnick & Fidell, 2013). In this study, one goal was to identify which dependent outcome variables (decomposed [deep] endophenotypes) best discriminated dichotomous trait motor impulsivity group membership (high or low trait motor impulsivity), including subscale membership. Consequently, one must calculate latent linear dimensions (linear variates, since MANOVA subscribes to the general linear model [GLM]) of the groups of dependent outcome variables for each laboratory behavioral measure to discriminate group membership (discriminate functions) via extraction of eigenvalues from eigenvectors (Field, 2013; Huberty & Olejnik, 2006; Meyers et al., 2017; Tabachnick & Fidell, 2013).

For this study, three dependent outcome variables were chosen (with two levels of each factor [independent predictor variable]) to ensure there was one linear variate (and one eigenvector) per study for each laboratory behavioral measure (top level endophenotype), since the number of variates is equal to the smaller of the number of dependent outcome variables, or the number of levels of the independent predictor variable minus one (Field, 2013; Huberty & Olejnik, 2006; Meyers et al., 2017; Tabachnick & Fidell, 2013). MANOVA is sensitive to outliers, which can create latent Type I and Type II errors (Tabachnick & Fidell, 2013). Consequently, univariate analysis of outliers, including Box plots and z-score analysis were run

for each cell of the design independently (Tabachnick & Fidell, 2013). However, taking a conservative approach, for the main analysis, all univariate and multivariate statistical outliers were retained to test and ensure robustness of the models to such outliers.

Cook's Leverage-Residual Sensitivity Analysis. With respect to multivariate outlier detection, while Mahalanobis distance (using eigenvalues) results were consulted and reported, Cook's distance was preferred to identify cases that disproportionately influence multivariate group comparison results (Cook, 1977). Mahalanobis distance thresholds were determined using chi-square critical values at $p < .001$, with degrees of freedom corresponding to the number of variables in each analysis, $\chi^2 = 27.88$, $df = 9$, for the global analysis across all nine dependent variables; $\chi^2 = 16.27$, $df = 3$, for each individual model analysis. The chi-square distribution is appropriate for Mahalanobis distance because this statistic follows a chi-square distribution under the assumption of multivariate normality, making chi-square critical values the standard method for establishing statistical significance thresholds for multivariate outlier detection (Tabachnick & Fidell, 2013).

While Mahalanobis distance is effective for detecting multivariately extreme values, it does not quantify a given case value's (participant's results) impact on group discrimination analysis and therefore was not used as a basis for case removal in the influence sensitivity analysis (Tabachnick & Fidell, 2013). Cases with materially influential discriminant values were removed in an influence sensitivity analysis to test model integrity and robustness and improve effect size and statistical significance by comparing results with influential outliers removed to those with influential outliers retained.

This influence sensitivity analysis approach (Cook's leverage-residual sensitivity analysis) measures how much overall MANOVA model estimates change upon case removal via

either case-weight perturbation of the model or covariate perturbation and is well suited for complex data structures in generalized linear (GLM) parametric models (Cook, 1977; Saleem et al., 2025; Tabachnick & Fidell, 2013; Zhu et al., 2012). The magnitude of Cook's distance is positively correlated with the magnitude of perturbation to the model via deletion of cases or a subset of observations (Zhu et al., 2012).

For the WCST, GNG, and SST models of this study, cases with Cook's distance values exceeding 0.0083 were flagged and labeled as having disproportionate influence on model parameter estimates. This threshold represents the point at which an individual case's removal (for this study, cases were removed across all three models for given exceeded thresholds in individual models, see below) would substantially alter the regression coefficients beyond what would be expected from random sampling variation (Cook, 1977). SPSS 30 implemented the calculation of Cook's distance values through the 'REGRESSION' procedure using the '/SAVE COOK' command, which automatically computed D_i for each case using the computational form of Cook's equation described below in the section on MANOVA mathematics. Cases exceeding the 0.0083 threshold were flagged for removal in the influence sensitivity analysis to assess model robustness and potential improvements in effect size and statistical significance.

It was expected that each model (WCST, GNG, SST) would have some flagged cases that were not flagged in other models. Consequently, it would be necessary to flag the aggregate number of threshold violating cases across the three models and then, as part of the influence sensitivity analysis, remove all the aggregately flagged cases from all three models so that any comparison of results across models or convergence of significant model outcome variables (selected features) as described below could be accomplished using the same sample space (case identity matrix). The procedure to do this involved creating a new master file for all three models

(WCST, GNG, SST) in SPSS 30 containing all nine dependent variables (features: PR, NPE, FMS, mRT, GNG_CE, GNG_OE, SSRT, SST_CE, SST_OE) and computing Cook's distance for each model one at a time. Next, the variable tag to Cook's distance for that model was renamed, and then a second and third Cook's distance calculation using the same renaming procedure was conducted. Finally, all cases exceeding Cook's threshold in at least one model were removed from all the models for influence sensitivity analysis. This aggregate removal was accomplished by creating a composite removal variable in SPSS' native syntax language using the logical OR function across all Cook's distance flag variables (e.g., `COMPUTE REMOVE_CASE = [COO_FLAG_WCST = 1 OR COO_FLAG_GNG = 1 OR COO_FLAG_SST = 1].`), ensuring systematic identification and removal of all cases flagged in any model. Once removal was completed, MANOVA's were run on the revised models and results compared to the master results and described accordingly.

Cross-Model Convergent Analysis. Following the completion of individual model main analyses (WCST, GNG, SST) and Cook's distance leverage-residual (influence) sensitivity analysis, a Cross-Model Convergent Analysis was designed to identify optimal decomposed endophenotype combinations for neurocomputational AI feature engineering and to validate the theoretical coherence of Barkley's three-facet behavioral response inhibition (BRI) theoretical framework. This analysis addresses a critical gap in the endophenotype literature discussed in Chapter 2 by systematically evaluating how decomposed endophenotypes from distinct laboratory behavioral task measures combine to maximize discriminative power for trait motor impulsivity (via Factor I motor impulsivity of the BIS-11 RDoC self-report and behavioral paradigms) while maintaining theoretical parsimony essential for feature engineering and

integration into AI digital twin and other neurocomputational machine learning and deep learning applications.

The Cross-Model Convergent Analysis employed four distinct analytical frameworks (Table 57), each testing different theoretical and empirical approaches to variable combination (Feature Engineering). Framework A (Optimal Performance) utilized all robust decomposed endophenotype candidates to maximize discriminative power. Framework B (Model-Representative) selected the strongest empirical performer from each laboratory behavioral model to test theoretical coherence across Barkley's three facets. Framework C (Attention-Focus) examined whether omission errors represent a core cross-model attention-deficit marker. Framework D (Theory-Empirical Hybrid) combined Barkley's theoretical framework with empirical robustness criteria.

Each framework was analyzed using MANOVA with the refined dataset (post-Cook's distance outlier removal) to compare high versus low BIS-11 Factor I Motor Impulsivity groups. Multivariate effect sizes, individual variable (feature) contributions, and statistical parsimony were evaluated to determine optimal decomposed endophenotype profiles for motor impulsivity classification in behavioral phenotypes. The analysis specifically sought to identify the minimal variable combination that maintains maximum theoretical coherence while achieving robust statistical discrimination—a critical requirement for AI neurocomputational applications where both accuracy and computational efficiency are paramount.

The following success criteria were established: (a) achieving multivariate significance at $p < .01$ with moderate effect sizes (partial $\eta^2 > .03$), (b) maintaining individual variable significance for included measures (features), (c) preserving theoretical alignment with Barkley's behavioral response inhibition (BRI) framework, and (d) optimizing parsimony for practical AI

neurocomputational model implementation. The comparative framework analysis was designed to provide definitive recommendations for feature engineering in neurocomputational models (digital twins) of behavioral phenotypes while advancing theoretical understanding of how decomposed endophenotypes integrate across cognitive domains to characterize motor impulsivity.

MANOVA Mathematics for This Study. A simplified mathematical perspective for the use of MANOVA for this study is provided below. Equations are provided solely to help demonstrate why MANOVA is an appropriate analysis to answer the research questions of this study. The description below will not provide mathematical details for assumption testing and ancillary and collateral statistical testing imbedded in SPSS. Nor will the description below provide mathematical derivations, particularly for linear and matrix algebra abstractions.

MANOVA was chosen for this study for several reasons. Among them are prior observations made in Chapter 2 that the psychological constructs being evaluated for this study are impulsivity and behavioral response inhibition as endophenotypes, which are not directly observable and thus comprise latent (hidden) variables. Their measures (through scales of the laboratory behavioral measures: GNG, SST, and WCST) are indicator (measured) variables (as proxies) of the latent variables (Meyers et al., 2017). The latent variables being measured by the WCST include neurobiological prefrontal cortical function, particularly of the dorsolateral prefrontal cortex (dlPFC), as previously discussed.

Linear combinations of the indicator variables (dependent outcome variables) are also latent variables (Meyers et al., 2017). Mathematically, such latent variables comprise a weighted composite (combination) of a plurality of measured indicator variables (three dependent outcome variables for each study [model of a laboratory behavioral measure] of this study) and are

typically referred to as variates (Myers et al., 2017). As described previously, they are linear variates in the context of the general linear model (GLM; Meyers et al., 2017; Huberty & Olejnik, 2006). Conceptually, such linear variates (weighted composites, wC) for each study (model) of this study can be represented by the general formula:

$$wC = w_1 dv_1 + w_2 dv_2 + w_3 dv_3 \quad (1)$$

where w_n represents some coefficient associated with the dependent variable dv_n (Myers et al., 2017).

Linear variates (and related eigenvectors and eigenvalues described in more detail below) are used in a number of advanced multivariate statistical methods including multiple regression (MR), exploratory factor analysis (EFA), confirmatory factor analysis (CFA), principal component analysis (PCA), structural equation modeling (SEM), canonical correlation analysis (CCA), path analysis (PA), generalized linear mixed models (GLMM), MANCOVA, linear discriminate analysis (LDA), discriminate analysis (DA), and MANOVA (Meyers et al., 2017). However, methods such as MR, EFA, CFA, PCA, SEM, CCA, and PA focus on the overall model performance, and not on the predictor independent variables (Meyers et al., 2017). LDA, DA, and MANOVA, on the other hand, focus on the amount of variance in the dependent outcome variables (indicator variable measures in this study comprising scales of the three laboratory behavioral measures) that is predicted by the effect associated with the categorical independent predictor variable (high and low BIS-11 Factor I trait motor impulsivity in this study) represented by the partial eta squared (partial η^2) effect size (Meyers, 2017).

Consequently, MANOVA and DA are most appropriate for this study. MANOVA was chosen due to the directionality of the desired analysis and classification of independent and dependent variables for this study. Mathematically, MANOVA and discriminate analysis (DA)

are not distinct, because the latter is the former in reverse (Tabachnik & Fidell, 2013). If the null hypothesis is rejected for a given research question (RQ) of this study, one or more dependent variables (or a combination of them) can predict a factor level (group membership), which discriminant analysis can be used to determine (Tabachnick & Fidell, 2013). DA is discussed further in the next section.

MANOVA tests whether the observed variance (between groups systematic variance) extracted from a matrix array (to generate a variance for the linear variate [composite]) in a given model (research question) exceeds the residual variance (within groups unsystematic residual variance; Huberty & Olejnik, 2006). In MANOVA, estimates of variances (determinants) are obtained from the sum of squares and cross-products variation matrices (SSCP; see below). In SPSS, MANOVA's output to determine significance of the differences in these variances is in the form of an approximate F value (statistic) using eigenvalues, where a high F value (and high eigenvalue representing a strong discriminant function) can generate a low p -value to support rejection of the null hypothesis (Field, 2013; George & Mallery, 2022; Huberty & Olejnik, 2006; Meyers et al., 2017).

Practically speaking, the MANOVA test F statistic can be calculated in SPSS via Pillai's Trace (Pillai-Bartlett trace), Wilks' Lambda, Hotelling-Lawley Trace, and Roy's Largest Root (Field, 2013; George & Mallery, 2022). The equations for each to calculate the F statistic, from which p -values are derived, are shown below without elaboration other than to demonstrate the variety of options for calculating the same statistic using subtly different mathematical approaches. Note that lambda [λ] represents an eigenvalue, as described further below:

Pillai's Trace:

(2)

$$v^{(s)} = \sum_{j=1}^s \theta_j = \sum_{i=1}^s \frac{\lambda}{1 + \lambda}$$

where λ represents the eigenvalue (see below) for each (s) discriminate variate,

Wilks' Lambda:

(3)

$$\Lambda = \prod_{j=1}^p (1 - \theta_j) = \prod_{i=1}^s \frac{\lambda}{1 + \lambda}$$

Hotelling-Lawley Trace:

(4)

$$T_g^8 = e \sum_{j=1}^8 \theta_j = \sum_{i=1}^s \lambda_i$$

Roy's Largest Root:

(5)

$$\left[F_{(2v_1+1, v_2+2)} = \frac{2v_1+2}{2v_2+2} \phi_{max} \right] = [\Theta = \lambda l]$$

where λl represents the largest eigenvalue for the first variate (the only variate for this study; Field, 2013; Huberty & Olejnik, 2006; Tabachnik & Fidell, 2013).

Pillai's Trace, Wilks' Lambda, and Hotelling-Lawley Trace are all variations of pooled ratio statistics (Field, 2013; Huberty & Olejnik, 2006; Tabachnik & Fidell, 2013; Popan, 2020, 27:50). Pillai's Trace comprises the pooled ratio of the effect variance to the effect variance plus the error variance (Popan, 2020, 27:50). Wilks' Lambda is the pooled ratio (of determinants) of the error variance to the effect variance plus the error variance (Popan, 2020, 27:50). Hotelling-Lawley Trace is the pooled effect variances (Popan, 2020, 27:50), or, more accurately, the sum of eigenvalues representing the ratio of between-group to within-group variance (Tabachnik & Fidell, 2013). Roy's Largest Root is not pooled and utilizes the variance from a dimension

(eigenvalue) that most significantly separates the group (Popan, 2020, 27:50). Roy's Largest Root is not generally recommended, but could have been used with this study, since there is only one dimension (and only one eigenvalue; see next paragraph; Field, 2013; Popan, 2020, 27:50).

SPSS calculated each of the above MANOVA significance test statistics (Field, 2013; George & Mallery, 2022). However, Wilks' Lambda was used as the primary method to calculate the F statistic for this study if there were equal sample groups and assumptions were met (Field, 2013; Huberty & Olejnik, 2006; Tabachnik & Fidell, 2013; Warner, 2013). Pillai's Trace was used as the primary method if there were unequal sample groups or if there were violation of assumptions, as it is considered the most robust in light of any violations of testing conditions, and assumptions (Field, 2013; Huberty & Olejnik, 2006; Tabachnik & Fidell, 2013; Warner, 2013). However, it was expected that the differences between the different calculations of the approximate F statistic would be similar, since there was only one linear variate (and one eigenvector and eigenvalue) due to each model (research question) containing only one independent predictor variable (factor) and two levels (groups) for each independent variable for each model as is described next (Field, 2013; Huberty & Olejnik, 2006; Tabachnik & Fidell, 2013). Consequently, all F statistic significance tests were reviewed and compared for this study.

From a latent variable perspective, conceptually, to calculate the variance from the matrix array, MANOVA utilizes eigenvectors (from linear and matrix algebra), corresponding to latent linear variates, to reduce (transform) matrix data complexity via their eigenvalue scaling factor, which consolidates the matrix variance (eigendecomposition; Hauser, 2016; Huberty & Olejnik, 2006; Tabachnik & Fidell, 2013; Williams, 2008). The eigenvector represents the base dimension (eigenbasis in a multidimensional array) of multivariate data and the eigenvalue (typically denoted as a scalar lambda $[\lambda]$) represents the magnitude of that dimension (Hauser,

2016; Huberty & Olejnik, 2006; Tabachnik & Fidell, 2013; Williams, 2008). In addition to F statistic significance tests, eigenvectors and eigenvalues are also used for MANOVA assumption testing, such as Mahalanobis distance and multivariate normality testing, to interrogate the distribution of eigenvalues in the correlation matrix or the covariance matrix, and in discriminate analysis (DA), as well as in principal component analysis (PCA) and other dimensional reduction methods discussed below as well as in Chapter 2 for neurocomputational methods that use statistical machine learning (Field, 2013; Huberty & Olejnik, 2006; Tabachnik & Fidell, 2013; Warner, 2013).

The data set for this study had multiple (two) predictor levels k of one factor (groups of an independent predictor variable) and multiple dependent outcome variables (three) p . The number of dimensions in the data is:

$$p \text{ if } p < k - 1 \text{ or } k - 1 \text{ if } k - 1 < p \quad (6)$$

Thus, for this study, the number of dimensions was one, which means one eigenvector and one eigenvalue (and one linear variate). A corollary of the focus of MANOVA for this study is essentially to decompose (via eigendecomposition) the matrix into its eigenvector and eigenvalue (Hauser, 2016; Huberty & Olejnik, 2013). The standard eigenvalue calculation for the eigenproblem is shown below:

$$\mathbf{A}v = \lambda v \quad (7)$$

Where the bold $\mathbf{A}$ represents a square matrix (using matrix algebra notation), λ the eigenvalue of $\mathbf{A}$, and v a non-zero eigenvector of $\mathbf{A}$ (Hauser, 2016; Huberty & Olejnik, 2013; Williams, 2008). Thus, the above mathematical expression indicates that a matrix-vector multiplication (a linear transformation) is the same as a scalar-vector multiplication. So, finding the values of λ (a scalar) and v (a vector) to make the above mathematical expression true

comprises the process of eigenvector and eigenvalue extraction (eigendecomposition; Hauser, 2016; Huberty & Olejnik, 2006; Williams, 2008). This can be done by converting the above mathematical expression into a pure matrix-vector multiplication using an identity matrix I , where:

$$I = \begin{pmatrix} \lambda & 0 & 0 \\ 0 & \lambda & 0 \\ 0 & 0 & \lambda \end{pmatrix} = \lambda \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \quad (8)$$

which revises the above mathematical expression to:

$$[\mathbf{A}v = (\lambda I)v] = [(\mathbf{A} - \lambda I)v = 0] \quad (9)$$

and then finding (solving for) a non-zero vector (an eigenvector v) that, when multiplied by the matrix, equals zero, which also involves finding a non-zero scalar (an eigenvalue λ ; Hauser, 2016; Huberty & Olejnik, 2006; Williams, 2008). In order for the matrix non-zero-vector product to equal zero, the determinant (a scaling factor for a linear transformation in linear algebra) of the matrix must equal zero (Hauser, 2016; Huberty & Olejnik, 2006; Williams, 2008):

$$DET(\mathbf{A} - \lambda I) = 0. \quad (10)$$

A determinate equal to zero enables identification of a matrix that reduces its state space into an area with a value of zero (Hauser, 2016; Huberty & Olejnik, 2006; Williams, 2008). The determinate of an $n \times n$ square matrix can be calculated using the Leibniz formula below:

$$DET(\mathbf{A}) = \begin{bmatrix} a_{1,1} & \cdots & a_{1,n} \\ \vdots & \ddots & \vdots \\ a_{n,1} & \cdots & a_{n,n} \end{bmatrix} =$$

$$DET(\mathbf{A}) = \sum_{\tau \in S_n} sgn(\tau) \prod_{i=1}^n a_{i,\tau(i)} = \sum_{\sigma \in S_n} sgn(\sigma) \prod_{i=1}^n a_{\sigma(i),i} \quad (11)$$

where sgn represents the permutation sign function for the permutation set S_n (a symmetric group representing the number of ways to arrange the matrix set) defined by the

function σ to reorder the set for an $n \times n$ matrix, and $\sigma \in S_n$ represents a permutation (i.e., a version of a matrix; Hauser, 2016; Huberty & Olejnik, 2006; Williams, 2008).

Conceptually, from the above equations, an eigenvector is a vector that will not change direction following a matrix-vector multiplication (i.e., following a linear transformation), but will change its magnitude, via a scalar (an eigenvalue; Hauser, 2016; Huberty & Olejnik, 2006; Williams, 2008). Because an eigenvalue reduces matrix dimensionality, it is used in MANOVA as a key test statistic for significance, such as Wilk's Lambda and Pillai's Trace, and assumption testing, such as Mahalanobis distance, as described previously (Huberty & Olejnik, 2006). Also because of that dimensional reduction, eigenvalues are used in dimensional reduction methods (discussed above and in Chapter 2 more generally) that can be used in post hoc MANOVA tests, as discussed in the next section (Huberty & Olejnik, 2006).

Because eigenvector and eigenvalue calculations require a square matrix, the eigenvector and eigenvalue for the matrix of this study could not be calculated directly without first constructing a square matrix by using a covariance or correlation matrix, since the matrix of this study is a non-square (rectangular) 2×3 matrix as shown below (Huberty & Olejnik, 2006):

$$\begin{pmatrix} k_1 & \cdots & Dv_n \\ \vdots & \ddots & \vdots \\ k_n & \cdots & Dv_n \end{pmatrix} \quad (12)$$

$$= \begin{pmatrix} k_1 & PR & NPE & FMS \\ k_2 & PR & NPE & FMS \end{pmatrix}, \begin{pmatrix} k_1 & mRt & CE & OE \\ k_2 & mRt & CE & OE \end{pmatrix}, \begin{pmatrix} k_1 & SSRT & CE & OE \\ k_2 & SSRT & CE & OE \end{pmatrix}$$

where k_n represents the number of levels of the factor (groups of the independent predictor variable) and Dv_n represents the number of dependent outcome variables. Thus, for this study, k_1 represents upper quartile Factor I BIS-11 trait motor impulsivity subscale scores and k_2 represents lower quartile Factor I BIS-11 trait motor impulsivity subscale scores; for the WCST,

PR represents preservative responses, NPE represents non-preservative errors, and FMS represents failure to maintain set; for the GNG, mRt represents mean reaction time, CE represents commission errors, and OE represents omission errors; and for the SST, SSRT represents stop signal reaction time, CE represents commission errors, and OE represents omission errors.

MANOVA is based on the general linear model:

$$Y = \beta X + \varepsilon \quad (13)$$

where Y is an $n \times m$ matrix of dependent outcome variables, X is a $n \times p$ matrix of independent predictor variables, β is a $n \times p$ matrix of regression coefficients and ε is a $n \times m$ matrix of residuals (Field, 2013; Huberty & Olejnik, 2006; Tabachnik & Fidell, 2013).

Calculation of the observed variance (and extraction of the eigenvalue from the eigenvector) of the model for each dependent variable (m_{Dvn}) starts with least square regression to calculate the sum of squares (SS; essentially the same equations as used in ANOVA) for each dependent outcome variable (between groups systematic variance) for each study (model) comprising a top-level research question (RQ; laboratory behavioral measure [WCST, GNG, SST]):

$$[\text{WCST}]: SS_{mDv1} = \sum n_k (\bar{x}_k - \bar{x})^2, SS_{mDv2} = \sum n_k (\bar{x}_k - \bar{x})^2, SS_{mDv3} = \sum n_k (\bar{x}_k - \bar{x})^2$$

$$[\text{GNG}]: SS_{mDv1} = \sum n_k (\bar{x}_k - \bar{x})^2, SS_{mDv2} = \sum n_k (\bar{x}_k - \bar{x})^2, SS_{mDv3} = \sum n_k (\bar{x}_k - \bar{x})^2$$

$$[\text{SST}]: SS_{mDv1} = \sum n_k (\bar{x}_k - \bar{x})^2, SS_{mDv2} = \sum n_k (\bar{x}_k - \bar{x})^2, SS_{mDv3} = \sum n_k (\bar{x}_k - \bar{x})^2$$

where k represents the levels (groups) of the factors (independent predictor variables), n represents the quartile (low Factor I trait motor impulsivity and high Factor I trait motor impulsivity) sample size for a given k factor level (so n elements of each k), and $\bar{x}_k$ is the mean of scores for a given dependent outcome variable for each factor level k , and $\bar{x}$ is the mean of the

scores for each dependent outcome variable across all k factor levels (two in this case; Field, 2013; Huberty & Olejnik, 2006; Tabachnik & Fidell, 2013).

Next, MANOVA calculates the sum of squares of the error (within groups unsystematic residual variance) as follows for each dependent outcome variable:

$$SS_E = \sum s_k^2(n_k - 1) \quad (15)$$

where s represents the variance of k . In other words, s represents each predicted value from $\bar{x}_k$ subtracted from the observed value for each element (participant) of k (Field, 2013; Huberty & Olejnik, 2006; Tabachnik & Fidell, 2013).

Next, MANOVA calculates the sum of squares total for each dependent variable as follows:

$$SS_T = \sum n_k(\bar{x}_k - \bar{x})^2 + \sum s_k^2(n_k - 1) \quad (16)$$

or

$$SS_T = SS_{mDvn} + SS_E. \quad (17)$$

Next, applying linear algebra and matrix algebra fundamentals, MANOVA calculates the sum of the cross-product covariance as follows:

$$SCP_{total} = SCP_{model} + SCP_{residual\ error} \quad (18)$$

where, for a 2 x 3 matrix of this study:

$$SCP_{model} = \sum_{g=1}^k n_k (\bar{x}_{g,dv1} - \bar{x}_{T,dv1})(\bar{x}_{g,dv2} - \bar{x}_{T,dv2})(\bar{x}_{g,dv3} - \bar{x}_{T,dv3}) \quad (19)$$

where n represents the number of participants (elements) in level k of each factor (independent predictor variable), g represents the group k (two levels for this study k_1 and k_2), dvn represents each dependent outcome variable for each study (three of each, in this case, for each laboratory behavioral measure [model or research question] dv_1 , dv_2 , and dv_3), and T

represents the total groupings (so, for example, $\bar{x}_{T,dv1}$, represents the total mean for dependent variable 1), and where:

$$SCP_{residual\ error} = \sum_{i=1}^n (\bar{x}_{i,dv1} - \bar{x}_{T,dv1})(\bar{x}_{i,dv2} - \bar{y}_{T,dv2})(\bar{x}_{i,dv3} - \bar{x}_{T,dv3}) \quad (20)$$

where i represents the score (subscale score [value] for each model [laboratory behavioral measure] for each dependent outcome variable) for each participant (element) and n represents the number of elements (participants) per level (Field, 2013; Huberty & Olejnik, 2006; Tabachnik & Fidell, 2013; Warner, 2013).

Next, MANOVA calculates the total sum of squares cross product matrices (total SSCP; using matrix algebra notation) where:

$$\mathbf{T} = \mathbf{H} + \mathbf{E} \quad (21)$$

where $\mathbf{T}$ represents the total sum of squares and cross-products variation matrix (total SSCP), $\mathbf{H}$ represents the hypothesis sum of squares and cross-products (between groups) variation matrix (hypothesis SSCP) and $\mathbf{E}$ represents the error sum of squares and cross-products (within groups) variation matrix (error SSCP; Field, 2013; Huberty & Olejnik, 2006; Tabachnik & Fidell, 2013). Thus, for this study, for each laboratory behavioral measure (model), $\mathbf{H}$ is described by the matrix:

$$\mathbf{H} = \begin{pmatrix} SS_{model,dv1} & SCP_{model,dv1 \times dv2} & SCP_{model,dv1 \times dv3} \\ SCP_{model,dv2 \times dv1} & SS_{model,dv2} & SCP_{model,dv2 \times dv3} \\ SCP_{model,dv3 \times dv1} & SCP_{model,dv3 \times dv2} & SS_{model,dv3} \end{pmatrix} \quad (22)$$

$\mathbf{E}$ is described by the matrix:

$$\mathbf{E} = \begin{pmatrix} SS_{residual,dv1} & SCP_{residual,dv1 \times dv2} & SCP_{residual,dv1 \times dv3} \\ SCP_{residual,dv2 \times dv1} & SS_{residual,dv2} & SCP_{residual,dv2 \times dv3} \\ SCP_{residual,dv3 \times dv1} & SCP_{residual,dv3 \times dv2} & SS_{residual,dv3} \end{pmatrix} \quad (23)$$

and $\mathbf{T}$ is described by the matrix:

$$\mathbf{T} = \begin{pmatrix} SS_{T,dv1} & SCP_{total,dv1 \times dv2} & SCP_{total,dv1 \times dv3} \\ SCP_{total,dv2 \times dv1} & SS_{T,dv2} & SCP_{total,dv2 \times dv3} \\ SCP_{total,dv3 \times dv1} & SCP_{total,dv3 \times dv2} & SS_{T,dv3} \end{pmatrix}. \quad (24)$$

It is the cross-product matrices that enable MANOVA to take into account any cross correlations between dependent outcome variables (Field, 2013; Huberty & Olejnik, 2006; Tabachnik & Fidell, 2013). This is a key reason described in the previous section for the selection of MANOVA for this study. Finally, SPSS calculates an approximate (for MANOVA, it is approximated, not actual) F statistic using eigenvalues (from Pillai's Trace or Wilks Lambda, for example) to determine whether there is sufficient statistical significance to reject the null hypothesis for a given research question (described at the beginning of this section) from the above matrices, and a p -value, to generate a statistically significant result (Field, 2013; Huberty & Olejnik, 2006; Tabachnik & Fidell, 2013; Warner, 2013). The practical significance (the effect) of a statistically significant result would then be provided by an effect size calculation.

Using Wilks' Lambda, the effect size for a one-way (one factor) between subjects unpaired MANOVA can be calculated using η^2 (η^2) to determine the proportion of variance that is predicted by the factor levels, as described below (Field, 2013; Huberty & Olejnik, 2006; Popan, 2020, 28:45; Tabachnik & Fidell, 2013; Warner, 2013):

$$\eta^2 = 1 - \Lambda. \quad (25)$$

Note that SPSS reports out a partial η^2 (partial- η^2) and not an η^2 (η^2) for MANOVA analysis expressed as

$$\eta^2 = 1 - \Lambda^{1/s} \quad (26)$$

$$\text{Where} \quad (27)$$

$$s = \sqrt{\frac{p^2 X (df_{effect})^2 - 4}{p^2 X (df_{effect})^2 - 5}}$$

where p represents the number of dependent outcome variables and df represents degrees of freedom, which equals the number of levels k (groups) minus one ($df_{effect} = k - 1$); because partial η^2 is generally preferred over η^2 and is considered a more conservative measure of effect size for MANOVA (George & Mallery, 2022; Tabachnik & Fidell, 2013; Warner, 2013). η^2 can overstate effects, whereas partial η^2 accounts for the number of dependent outcome variables (George & Mallery, 2022; Tabachnik & Fidell, 2013; Warner, 2013).

Post Hoc Tests. If MANOVA yielded a statistically significant result for a major research question (i.e., the multivariate null hypothesis was rejected), post hoc analysis of the secondary research questions was conducted to determine the strongest contributor to group differences (levels of factors comprising dichotomous independent predictor variables) among the dependent outcome variables. There are a number of possible post hoc analysis that can be conducted following a MANOVA analysis. For example, Bonferroni Correction can be done, which performs a plurality of t -tests on each pair of groups by dividing the significance level by the number of comparisons to normalize or recapture the pre-compounded Type I error rate, followed by independent samples t -test to identify differences between pairs (Field, 2013; Tabachnick & Fidell, 2013). Somewhat similar post hoc analysis includes Tukey's Honest Significant Difference (HSD) and Scheffe's Test (Field, 2013; Tabachnick & Fidell, 2013).

However, more common in MANOVA are post hoc tests that could have been used as primary tests, including discriminant analysis (DA) and principal component analysis (PCA), and canonical correlation analysis (CCA), each of which use eigenvalues; multiple ANOVAs (one for each dependent variable), and t -tests (Al-Abdullatif et al., 2019; Huberty & Olejnik,

2006; Tabachnick & Fidell, 2013; Warne, 2014). Often, the mathematically most appropriate and recommended post hoc analysis is a discriminate analysis (DA; Al-Abdullatif et al., 2019; Warne, 2014). DA provides a series of perfectly uncorrelated linear equations to elucidate differences among the two factor levels (dichotomous groups; Al-Abdullatif et al., 2019; Huberty & Olejnik, 2006; Warne, 2014). As mentioned in the previous section, discriminate analysis is the inverse of MANOVA. Consequently, DA can be used to interrogate the dependent variables as predictors of group membership. However, DA maintains the groupings of dependent variables to predict group membership, rather than extracting one or more dependent variables (Tabachnick & Fidell, 2013). DA also interrogates the pattern of differences among dependent variables to identify latent dimensions that characterize those differences (Tabachnick & Fidell, 2013).

This study (through the sub-research questions) sought to decompose significant linear variates to identify the dependent outcome variable most strongly predicted by group membership. Further, as mentioned above, there is only one linear variate (and eigenvector and eigenvalue) for each study (laboratory behavioral measure), since there are only two levels of the factor (two groups of the independent predictor variable) and three dependent outcome variables per study (laboratory behavioral measure). Consequently, there can only be one discriminate linear equation (and one eigenvector and eigenvalue) per study or model (laboratory behavioral measure) for this study, so DA was deemed unnecessary to answer the sub-research questions.

Multiple ANOVAs are also often used for post hoc analysis of MANOVA tests (Al-Abdullatif et al., 2019; Warne, 2014). As discussed above, multiple ANOVAs increase Type I errors (false positives), since the probability of at least one Type 1 error in at least one ANOVA in a series of ANOVAs is up to $1 - (1 - \alpha \text{ value})^{\text{number of ANOVAs}}$ (Huberty & Olejnik, 2006;

Warne, 2014). This Type I inflation also occurs when performing multiple independent samples *t*-tests, although this can be controlled via Bonferroni Correction (Warne, 2014). However, Bonferroni Correction becomes increasingly conservative as the number of tests and correlated variables increase (Huberty & Olejnik, 2006; Warne, 2014). This is one reason Bonferroni Correction was not chosen as a post hoc analysis for this study. Multiple ANOVAs are typically inappropriate to perform as tests of main effects in cases of multiple dependent variables due to Type I error compounding, where MANOVAs are more appropriate, and ANOVAs are often inappropriate to perform as post hoc tests as well. Note, that if the independent predictor variable (factor) is dichotomous (there are only two categorical groups or levels), then one-way ANOVA simplifies to an independent samples *t*-test (Huberty & Olejnik, 2006; Warne, 2014).

However, while following a MANOVA analysis (a multivariate test) by a post hoc ANOVA analysis (a univariate test) is often inappropriate to interrogate multivariate effects, the dichotomous nature of the independent predictor variable and the limitation of dependent variables per study to three, results in only one linear variate (and one eigenvector and eigenvalue) per study and only one discriminate linear equation per study. Therefore, under the assumption that post hoc multivariate discriminate analysis, where there is only one linear variate and one discriminate function equation per study, will not provide substantially more information than an independent ANOVA, once the multivariate hypothesis is rejected for a given study (top line research question), each dependent variable can be evaluated independently using an ANOVA, which reduces to an independent samples *t*-test, since there are only two distinct and unique categorical groups (Huberty & Olejnik, 2006; Warne, 2014).

Consequently, the post hoc analysis conducted for this study was an independent samples *t*-test (independent-measures *t*-test; Field, 2013). In light of the above assumptions, the

independent samples t -test is an appropriate post hoc analysis to answer each of three sub-research question for each model (research question, study, or laboratory behavioral measure), because there are two dichotomous groups (levels) of the independent predictor variable (factor; Field, 2013). Conceptually, an independent samples t -test takes the observed difference between sample means on each dependent outcome variable for each level (group) for each model (study or research question corresponding to each laboratory behavioral measure [WCST, GNG, SST]) and subtracts the expected difference between population means for that dependent outcome variable given a failure to reject the null hypothesis, and divides that result by the estimate of the standard error of the difference between the two sample means (Field, 2013). Mathematically, this concept is expressed as follows: (28)

$$t = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{s_1^2}{N_1} + \frac{s_2^2}{N_2}}}$$

where $\bar{X}$ in the numerator represents the sample means for a given dependent outcome variable, and the denominator represents the standard deviation of the sampling distribution of the population, which represents the standard error of sampling distribution of the differences (Field, 2013). Note that, if the sample size (elements) of each level of a factor (independent predictor variable) differs, then a pooled variance estimate t -test can be used that uses a weighted (by its degrees of freedom) average divided by the sum of weights as a sum of both degrees of freedom (Field, 2013). This study sought to maintain equal numbers of elements (sample size) by using quartiles to determine group membership to avoid this added complication.

Note further, however, that while an independent samples t -test can identify which dependent outcome variable most strongly contributes to between groups differences

independently, it cannot provide which combination of any two variables out of three best discriminates the dichotomous groups. Discriminate analysis would be appropriate for the latter. However, this study does not include additional research questions to evaluate combination of pairs of dependent variables post hoc to a MANOVA analysis of the primary research questions. Consequently, DA was not evaluated for this study.

Cook's Leverage-Residual Sensitivity Analysis. As previously discussed, discrepant outliers were labeled using Cook's distance to identify the most influential outliers within cases for removal (the model perturbation). Cook's distance equation can be expressed purely mathematically or computationally (Cook, 1977; Saleem et al., 2025; Zhu et al., 2012). For a given model (WCST, GNG, SST), given 480 cases for the study group (see Chapter 4), Cook's distance for the i^{th} case is defined as:

$$D_i = \frac{(\hat{\beta} - \hat{\beta}_{(i)})^T (\mathbf{X}^T \mathbf{X}) (\hat{\beta} - \hat{\beta}_{(i)})}{p \cdot \frac{\sum_{j=1}^n (y_j - \hat{y}_j)^2}{n - p}} \quad (29)$$

which simplifies to (30)

$$D_i = \frac{(\hat{\beta} - \hat{\beta}_{(i)})^T (\mathbf{X}^T \mathbf{X}) (\hat{\beta} - \hat{\beta}_{(i)}) \cdot (n - p)}{p \cdot \sum_{j=1}^n (y_j - \hat{y}_j)^2}$$

where D_i = Cooks distance for the i^{th} observation; $\hat{\beta}$ = the vector of regression coefficients estimated with all cases included (i.e., $n = 480$); $\hat{\beta}_{(i)}$ = the vector of regression coefficients with case i removed; $\mathbf{X}$ = the design matrix of predictor variables; p = the number of parameters (2 [intercept and group effect] per dependent outcome variable per model) in the model, including

the intercept; n = total sample size (480 per model for this study), y_j = the observed value for case j ; $\hat{y}_j$ = the predicted value for case j ; $\mathbf{e}$ = the vector of residuals ($y_j - \hat{y}_j$); and (31)

$$\sum_{j=1}^n (y_j - \hat{y}_j)^2 = \frac{\mathbf{e}^T \mathbf{e}}{n - p} = MSE$$

where MSE = mean square error from the entire model.

Practically speaking, SPSS uses a matrix algebra transformed computational form of the above Cook's distance equation for computational efficiency. The computational form avoids re-fitting the model n times, uses readily available regression diagnostics (see r_{ii} and h_{ii} below), and illustrates the dual influence of residuals and leverage explicitly, effectively making the computational form computationally more efficient to execute and iterate as it does not require dropping cases and re-estimating parameters repeatedly (Cook, 1977; Cook & Weisberg, 1982). The computational form of Cook's distance equation can be derived by expressing the parameter difference ($\hat{\beta} - \hat{\beta}_{(i)}$) in terms of standardized residuals and leverage values through matrix algebra to the form (32)

$$D_i = \frac{r_i^2}{p} \cdot \frac{h_{ii}}{(1 - h_{ii})^2}$$

where the matrix transformation resolves Cook's distance as a product a residual component and a leverage component, where the residual component r_i^2 / p indicates how poorly the model fits case i and the leverage component $h_{ii} / (1 - h_{ii})^2$ indicates how extreme (how far from the centroid) case i 's predictor values are; where r_i = standardized residuals for case i ; h_{ii} = leverage value (the diagonal element of the hat matrix) for case i ; and p = the number of parameters (again 2 [intercept and group effect] per dependent variable [DV] per model).

The threshold used to identify influential outliers for Cook's distance for this study is based on the F -distribution percentile that corresponds to cases having substantial influence on parameter estimates, providing a balance between sensitivity to outliers and retention of legitimate extreme values that represent natural population variation (Cook, 1977). Thus, the formula for the Cook's distance threshold (DT) is simply

(33)

$$Cook's\ DT = \frac{4}{n}$$

where n = the total sample size, which equals 480 (240 for each dichotomous predictor variable treatment group of high BIS-11 FI-MI and control group of low FI-MI) for each model of this study (Cook, 1977; Tabachnick & Fidell, 2013). Thus, Cook's threshold used for the influence sensitivity analysis for this study was 0.0083 (i.e., 4/480).

Assumptions

There are numerous assumptions made by this study. First, Qualtrics GenPop (general population) research panels are targeted to represent a broad demographic of age, race, ethnicity, and socioeconomic status. Consequently, it was assumed that the Qualtrics research panel was representative of the general population for, initially, males 18-34, and following pilot testing, 18-40 males and females. Related to this is the assumption that the sample will comprise a distribution of participants with levels of impulsivity and neurotypical and pathological levels of mental functioning as is represented in, and thus generalizable to, the general population for 18–34-year-old males and 18–40-year-old males and females, respectively. Second, it was assumed that participants would respond to both screening questions and BIS-11 self-report questions honestly and deliberately, as failure to do so could render results meaningless or provide false

results. In particular, it was assumed that each participant would accurately self-report a history of impulsivity or lack thereof (assuming test-retest reliability implicit in the BIS-11). Third, it was assumed that all participants would be attentive during each measure with minimal distraction and similar testing conditions, including influences from sleep, diet, and stress levels, all of which can influence attentiveness and response variables. Fourth, it was assumed that the demographic cultural distribution of a sample United States population was representative of the global demographics, since most United States residents are immigrants or descendants of immigrants. Finally, it was assumed that measures of face, content, construct, and criterion validity of each instrument implemented for this study were similar to that reflected in the research literature for each instrument.

Limitations

There are numerous limitations to this study, including challenges and threats to the validity of this study. Among general limitations, the assumption noted above that Qualtrics research panels may represent a broad demographic of the target population may not be accurate. While Qualtrics indicates that it recruits GenPop (general population) panel membership from a variety of sources, it does not typically provide precise information regarding the nature of their sampling frames and recruitment (Miller et al., 2020). Consequently, the sample may not represent the study population to the extent assumed and comprise a sampling bias. Efforts were made to mitigate this limitation by requesting as much information regarding methods of panel recruitment from Qualtrics as suggested by Miller et al. (2020). Participant self-selection into Qualtrics research panels also represents a limitation, contributing to sampling bias. Mitigation of this limitation aligns with the above inquiry to Qualtrics to some extent. It is also possible that individual participants may have attempted to undertake the study multiple times to maximize

economic benefit. This was mitigated using Qualtrics features to permit only one participation per unique participant and a unique participant numerical identifier and carefully and systematically filtering out duplicate results from the same participant numerical identifier.

The inability to control for a plurality of confounding variables is also a limitation. These include DSM or neurological diagnosis or undiagnosed conditions (particularly externalizing disorders with impulsivity or compulsivity as key symptoms) and use of medications that can influence outcome measures on laboratory behavioral measures, but not self-report measures (or vice versa), which can contribute to false or misleading results. While it was difficult to mitigate this limitation, collection of information regarding DSM related diagnosis and the use of certain medications and an assumption regarding distribution of psychopathology and neurological conditions in the sample as compared to the general population provided some measure of mitigation that also permits future analysis of compounders and covariates.

Participants may have also responded dishonestly or in a manner attempting to respond in a way a participant anticipates the researcher wished the participant to respond, particularly as biased by repeated measures. This may negatively affect validity, which is discussed in the next few sections. Mitigation was made by use of instructions that reinforced participants to answer honestly and without influence, supported by anonymity and utility of the consequences of honest and uninfluenced reporting.

Finally, the sample comprised United States based participants. Consequently, cultural differences were not captured. While, arguably, cultural differences may be mitigated via the assumption that a United States demographic represents a globally originated cultural demographic that is representative of the full diversity of global cultures, there are two factors that limit any mitigation by this assumption. First, numerous studies have demonstrated that

immigrants or descendants from other cultures absorb local cultural norms, which includes behavioral adaptations at the neural level due to gene-environment interactions (Chiao & Immordino-Yang, 2013; Harada et al., 2020; Kuipers & Thierry, 2015). Second, dopaminergic systems and genes implicated in impulsivity have evolved differently in different populations. For example, the dopamine receptor DRD4-7R allele discussed in Chapter 2 is often associated with novelty seeking and impulsivity and has a higher prevalence among Americans than in other countries and is particularly prevalent among native American populations (Chang et al., 1996; Ding et al., 2002; Kidd et al., 2014). This can be at least partially explained by the premise that those individuals who immigrate from their places of origin to far away domiciles of unknown efficacy and safety are more likely to exhibit novelty seeking and dopaminergically driven or seeking impulsive behavior (Change et al., 1996; Ding et al., 2002; Kidd et al., 2014).

External Validity. As discussed in the next section on delimitations, the sample of males ages 18-34, initially, and males and females ages 18-40, following pilot testing, was chosen because these groups are most likely to exhibit stable impulsivity traits and behaviors versus individuals under 18, who tend to exhibit more impulsivity as age decreases and over 34 and 40 who tend to exhibit less impulsivity as age increases. Further, males tend to exhibit more impulsivity, generally, than females (Cross et al., 2011). While this maximizes the trait measures in the groups, it cannot be generalized to females (which was mitigated following addition of females after pilot testing) or to all ages. Further, a key population in the behavioral phenotypes that may be informed by the results of this study are ADHD and ASD patients, who tend to be under 18 in the clinical literature. However, this may be mitigated since, as discussed in Chapter 2, both conditions continue to a material extent into adulthood, and the advantages of limiting the sample to this group may outweigh broader generalizations. Somewhat similarly, the prevalence

of BPD in clinical populations is predominantly female (as much as 76%), a population not initially included in this study, but added following pilot testing in this study, although the literature suggests closer to an equal distribution of prevalence of BPD among males and females in the general population (Silberschmidt et al., 2015). Further, there may be some measure of generalizability to these populations that can be tested or explored further in these excluded groups.

Internal Validity. Threats to internal validity include confounding variables, instrumentation, and testing (Trochim et al., 2015). Confounding variables include undetermined behavioral phenotype comorbidities, possible use of stimulants by participants, distractions during testing, and time of day for testing, which can all influence state impulsivity. These could have been mitigated to some extent through instructions that suggest participants are well fed and rested and minimize distractions during testing. Challenges with instrumentation includes the selection of the individual measures (subscales of the WCST, GNG, and SST), which appear less in the literature than top line measures, and parameter settings (e.g., time delay between stimulus), since parameter settings vary. Testing challenges included testing conditions and timing of testing. Confounding variables may have also been minimized via the large sample size, which also helped reduce testing issues by increasing sensitivity. Also, instrumentation challenges were reduced by selecting parameters for each measure that are most well supported in the impulsivity/behavioral response inhibition literature.

Construct Validity. Threats to construct validity included each individual measure selected to measure given facets of behavioral response inhibition and trait impulsivity (Trochim et al., 2015). Participant acclimation to repeated measures also presented a threat. The former threat was reduced by selecting measures and subscales supported by the literature to measure

the facets of behavioral response inhibition or trait impulsivity, respectively. Repeated measures threats were minimized via randomizing or subjectively varying the order of laboratory behavioral measures.

Conclusion Validity. Threats to conclusion validity included both Type I (a false positive observing a difference where none exists) and Type II (a false negative where no difference is detected where one exists; Trochim et al., 2015). This threat was addressed via sample size to increase statistical power and study design (e.g., using top and bottom quartiles to ensure a measurable difference in groups of low and high trait motor impulsiveness).

Delimitations

Initially, males were chosen to control for confounding effects of sex on baseline levels of impulsivity and to maximize measurable levels of impulsivity to best address the problem of this study. The literature indicates that, as a population, males demonstrate higher levels of baseline impulsivity than females (Allen et al., 2022; Chamorro et al., 2012; Cross et al., 2011; Ramtekkar et al., 2010). Further, males and females demonstrate distinct genetic etiology across the lifespan to different facets of impulsivity and deficits in BRI (Niv et al., 2012). Consequently, the initial design included a focus on one population to better align with the goal of differentiating facets of impulsivity and BRI independent of sex differences. However, as noted above, females were added to improve study yield, and such addition did make results more generalizable. Further, females better represent clinical BPD samples.

The age range of 18-34 (and, following pilot testing, 18-40) was chosen to ensure the most consistent and stable baseline impulsivity levels to reduce the confounding effects of age on baseline levels of impulsivity and deficits in behavioral response inhibition. To start, adults are more likely to be accurate self-reporters than adolescents and children, who tend to lack as much

insight into their behavior or predispositions as adults do (Reynolds et al., 2006). The literature also indicates that children and adolescents exhibit both the highest levels of baseline impulsivity and related constructs and most dramatic changes over a developmental time series (Chamorro et al., 2012; Ramtekkar et al., 2010; Steinberg et al., 2008). Further, differential impulsivity types and disinhibition develop along distinct and very dynamic trajectories. While cognitive impulsivity increases during adolescence versus childhood and adulthood, disinhibition decreases from childhood into adolescence and adulthood as executive functions of cognitive control develop in the prefrontal cortex and go fully on-line by mid young adulthood (Niv et al., 2012). Consequently, from childhood to adolescence to adulthood, measures of impulsivity and behavioral response inhibition may vary, in large part, due to differences in developmental trajectories of their distinct neural correlates. By minimizing the confounding impact of these trajectories by selecting an age range where their differences are minimized, more consistent results can be obtained.

Finally, adults over the age of 34 (and 40) demonstrate, at the population level, a more accelerated decrease in impulsivity than the sample group (Chamorro et al., 2012). This is not to suggest that adults over 34 (and 40) do not exhibit measurable levels of impulsivity, including dysfunctional impulsivity, or that deficits in BRI may not be more problematic in older adults than even adolescents. However, that variation, even in light of decreasing overall levels of certain types of impulsivity and BRI, in impulsivity above age 34 (and 40), is greater than variation in the sample group, including variation in neural correlates of various impulsivity subtypes and BRI features (Morales-Vives & Vigel-Colet, 2012).

Ethical Assurances

This study was of minimal risk to participants and received approval from Northcentral University's Institutional Review Board (IRB) prior to commencement (or change) of data collection (Appendix A). This study utilized informed consent procedures consistent with protocols and IRB requirements for ethical studies. This included a click through verification that required consent be given after review of the informed consent document where those that did not verify consent were not permitted to continue and were excluded from this study.

Answers to screening questions and results of BIS-11 and laboratory behavioral assessments were de-identified, including IP addresses, and kept strictly confidential using a secure web-portal via Qualtrics, which includes ISO 27001 data encryption and data security and secure external hard drive with password protection. In each case, psychometric measures were made using the well-established protocols of those measures.

The role of the researcher in this study was non-interactive with study participants unless there were questions or issues from participants or with data collection. The researcher has ADHD and three children with ADHD and one child with ASD. To minimize implicit bias, the method, results, and analysis of results were reviewed and approved by a three-member dissertation committee, including one or more subject matter experts.

Summary

This chapter presented the methodological framework for a quantitative quasi-experimental ex post facto study examining relationships between trait motor impulsivity on the BIS-11 and laboratory behavioral measures of behavioral response inhibition (BRI). The problem addressed by this study was that the endophenotype literature does not adequately characterize and segregate the dimensionality of the latent psychological constructs of

impulsivity and impulse control (i.e., behavioral response inhibition [BRI]). The purpose of this quantitative quasi-experimental ex post facto study was to discriminate neurobiological and neuropsychological measures through assessing the relationships between subscales of the Barratt Impulsiveness Scale (BIS-11) for low and high Factor I trait motor impulsivity and subscales of three laboratory behavioral measures of BRI, the go/no-go task (GNG), stop signal task (SST), and Wisconsin card sorting test (WCST). This quantitative quasi-experimental ex post facto study had multiple dependent outcome variables and dichotomous independent predictor variables (factor levels) comprising two groups.

The nature of this study was that of a quantitative study following the Research Domain Criteria (RDoC) promulgated by the National Institute of Mental Health (NIMH) division of the National Institutes of Health. A quantitative study design was appropriate because the associations that were to be determined by this study were empirically measurable and could be quantified with a measure of precision. The study design is quasi-experimental because non-probability convenience sampling was used and not all confounding variables controlled (including the presence of latent variables; Leedy & Ormrod, 2013).

This study included three categories of measurements, (a) a psychometric self-report measure of trait impulsivity, with a focus on measures of self-reported trait motor impulsivity, (b) a laboratory behavioral measure used as a proxy for neuroanatomical and neurofunctional locus (a neurobiological correlate) related to disinhibition (lack of impulse control), and (c) laboratory behavioral measurements of state motor impulsivity and behavioral response inhibition (neuropsychological correlates). As a pretest measure to determine experimental and control groups, initially, male participants ages 18-34, and, following pilot testing, male and female participants ages 18-40 completed the BIS-11 self-report questionnaire on-line via a

Qualtrics enabled and hosted gateway. Outcome measures on the BIS-11 subscales relating to motor impulsivity were used as the criteria for grouping of treatment and control groups. Each participant was then administered (i) the Wisconsin card sorting test (WCST) as a measure of neuroanatomical function that relates to behavioral response inhibition (BRI) and (ii) two laboratory behavioral measures, the go/no-go task (GNG) and the stop-signal task (SST), of behavioral response inhibition (state impulsivity) that putatively or theoretically test at least two facets or phase states of trait impulsivity.

Each primary research question corresponded to one of the laboratory behavioral measures (models) of this study, which are among RDoC (paradigm) units of analysis. Each research question also had three sub-questions to support post hoc analysis of each dependent outcome variable comprising a subscale of each laboratory behavioral measure (model). Thus, each of the main research questions asked whether linear variates of three sub-scales (facets, components, features, factors) of each laboratory behavioral measure differed between the dichotomous high and low groupings (levels) of BIS-11 sub-scales for Factor I trait motor impulsivity (independent predictor variables as factors). Each post hoc analysis then answered each sub-question, namely, which sub-scale associated most strongly with differences in BIS-11 trait motor impulsivity sub-scale scores.

The approach to addressing and aligning with the problem of this study sought to develop a nomological network of the dimensions of motor impulsivity as a latent variable through observational instrumental sub-measures that segregated those dimensions, a process referred to for the purposes of this study as RDoC latent variable endophenotype decomposition. This approach is consistent with RDoC's top-down approach. Such decomposed endophenotypes can also inform research on so called phenologs, which are orthologous phenotypes (or

endophenotypes) that can inform differential research of DSM behavioral phenotypes (de Vienne, 2022). Decomposed endophenotypes can also better inform more complex studies, such as the generic model study in Chapter 2 that include genotyping and/or neuroimaging and neurophysiological measures and measures of behavioral phenotypes, and decomposed endophenotypes can also provide validated inputs for neurocomputational models (digital twins) of behavioral phenotypes, including, ADHD, ASD, schizophrenia, and BPD.

The target population under study was adult putative neurotypical males and females ages 18-40. DSM diagnosis was neither controlled for nor excluded. This population (30%-34% of the male population, and 30%-36% of the female population) represented an age range that is more consistent with respect to impulsivity that also represents the age cohort commonly used to norm the measures used for this study (Chamorro et al., 2012).

A G*Power power analysis generated a preliminary minimum sample size of 280 for an actual power of .95. However, because the dichotomous groupings (levels) comprised the top and bottom quartile scores on the BIS-11, the total sample size targeted was between 560-600 to permit sufficient powering of the top and bottom quartile scores.

This study utilized a Qualtrics research panel to recruit study participants using non-probability convenience sampling after certain inclusion and exclusion criteria were met. Data was collected using a Qualtrics gateway with a forwarding link to a portal hosting on-line versions of the self-report and laboratory behavioral instruments through the Inquisit 6 web data software package from Millisecond Software. The screening questionnaires, informed consent, self-report measure, and all laboratory behavioral measures can be completed in approximately 30 minutes or less.

Certain scale and subscale scores were collected for each instrument. For the BIS-11 instrument, top and bottom quartile subscale scores of trait motor impulsivity were collected to determine the dichotomous independent predictor variable groupings (factor levels), including Factor I and Factor II BIS-11 subscale scores. A cut off for BIS-11 total score is putatively 72 (the upper quartile would actually be used) to indicate highly impulsive individuals and 57 for low impulsive individuals, which approximates one standard deviation and a score below 52 was evaluated for outliers to exclude certain participants as erroneous or dishonest responders. Observed top and bottom quartile scores were used for Factor I and Factor II trait motor impulsivity.

A one-way (one-factor) between subjects unpaired multivariate analysis of variance (MANOVA) was used to assess the differences among composite means of linear variates of the laboratory behavioral measures comprising dependent outcome variables from each instrument for each level of the factor for each study. MANOVA was used because there was one independent grouping variable (two level factor) and multiple dependent outcome variables for each instrument and a comparison of linear variates of composite means of the dependent outcome variables (Field, 2013; Huberty & Olejnik, 2006; Tabachnick & Fidell, 2013). MANOVA can also detect differences between groups along a plurality of dimensions, in this case various instrumental subscales or facets (endophenotypes; Field, 2013; Huberty & Olejnik, 2006; Tabachnick & Fidell, 2013). MANOVA also improves power and effect size by taking into account cross correlations between dependent variables (Field, 2013; Huberty & Olejnik, 2006; Tabachnick & Fidell, 2013). MANOVA also tests differences in latent variables, such as the constructs of impulsivity and behavioral response inhibition and their facets (Warne, 2014).

A post-hoc independent samples *t*-tests (or Welch's *t*-test if assumptions were violated) was conducted, if results were statistically significant, to identify the source of the differences and thus, to identify novel decomposed endophenotypes (Schumacker & Lomax, 2010). While discriminate analysis (DA) is often suggested as the most appropriate post hoc analysis for a MANOVA (Al-Abdullatif et al., 2019; Warne, 2014), because there was only one linear variate for each study (laboratory behavioral measure), since there were only two levels of the factor (two groups of the independent predictor variable) and three dependent outcome variables per study (laboratory behavioral measure), there can only be one discriminate linear equation per study (laboratory behavioral measure) for this study. Consequently, arguably, independent ANOVAs can be run for each dependent variable post hoc rather than DA, since only individual contributions of dependent variables were assessed. If the independent predictor variable is dichotomous (there are only two categorical groups), then one-way ANOVA simplifies to an independent samples *t*-test (Warne, 2014) or Welch's *t*-test, explaining their use for this study.

Following the main MANOVA analyses, a Cook's leverage-residual (influence) sensitivity analysis was conducted to identify cases that disproportionately influenced multivariate group comparison results and to test model robustness. Cases with Cook's distance values exceeding 0.0083 in any model were removed from all three models to ensure consistent sample space for cross-model comparisons. MANOVA analyses were then re-run on the refined datasets and results compared to the original analyses to assess model integrity and potential improvements in effect size and statistical significance.

A Cross-Model Convergent Analysis was designed and implemented following Cook's distance influence sensitivity analysis to identify optimal decomposed endophenotype combinations for neurocomputational AI feature engineering for neurocomputational models

(digital twins) of behavioral phenotypes and to validate the theoretical coherence of Barkley's three-facet behavioral response inhibition framework. This analysis employed four distinct analytical frameworks: Framework A (Optimal Performance) utilizing all robust decomposed endophenotype candidates; Framework B (Model-Representative) selecting the strongest empirical performer from each laboratory behavioral model; Framework C (Attention-Focus) examining omission errors as a cross-model attention-deficit marker; and Framework D (Theory-Empirical Hybrid) combining Barkley's theoretical framework with empirical robustness criteria. Each framework was analyzed using MANOVA with the refined dataset generated by the Cook's analysis to compare high (treatment) versus low (control) BIS-11 Factor I Motor Impulsivity groups. This study included a plurality of assumptions that may not have been met or limitations that may not have been successfully mitigated if at all, including threats to various types of validity. This study was of minimal risk to participants and received approval from Northcentral University's Institutional Review Board (IRB) prior to commencement of data collection (Appendix A).

Chapter 4: Findings

The problem addressed by this study was that the endophenotype literature does not adequately characterize and segregate the dimensionality of the latent psychological constructs of impulsivity and impulse control (i.e., behavioral response inhibition [BRI]). The purpose of this quantitative quasi-experimental ex post facto study was to discriminate neurobiological and neuropsychological measures through assessing the relationships between subscales of the Barratt Impulsiveness Scale (BIS-11) for low (control group) and high (treatment group) trait motor impulsivity and subscales of three laboratory behavioral measures of BRI, the go/no-go task (GNG), stop signal task (SST), and Wisconsin card sorting test (WCST). This quantitative quasi-experimental ex post facto study had multiple dependent outcome variables and a dichotomous independent predictor variable comprising two groups (factor levels). Consequently, a one-way (one-factor) unpaired between subjects multivariate analysis of variance (MANOVA) was used to assess the differences among composite means of linear variates of a set of laboratory behavioral measures comprising dependent outcome variables from each instrument for each level for each study. A post-hoc independent samples *t*-test (or Welch's *t*-test if assumptions were not met) was conducted, if results were statistically significant, to identify the source of the differences and thus, to identify novel decomposed endophenotypes (Schumacker & Lomax, 2010). Following the main analysis, a Cook's distance leverage-residual (influence) sensitivity analysis was conducted to test model robustness and improve effect size and power. A cross-model convergent analysis was designed and conducted following influence sensitivity analysis to identify the most efficient grouping of features for neurocomputational AI digital twin models of behavioral phenotypes.

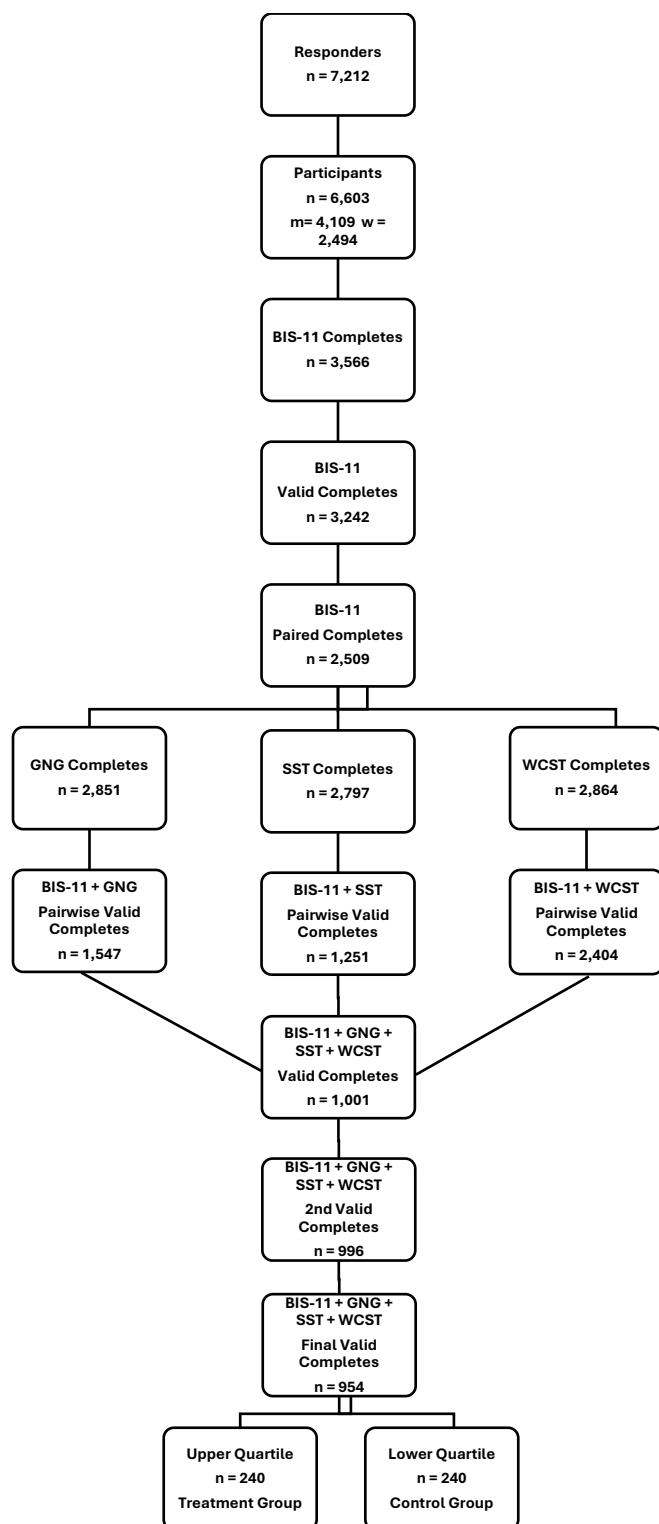
The following sections of Chapter 4 include Data Collection, Data Pre-Processing, Study Demographics, Study Group Data, Validity and Reliability of the Data Generally, Research Question 1 (RQ1), H1, The Wisconsin Card Sorting Test (WCST); Research Question (RQ) 2, H2, The Go/No-Go (GNG) Model; Research Question 3 (RQ3), H3, The Stop Signal Task (SST) Model; Implementation of Cook's Leverage-Residual Sensitivity Analysis, Implementation of Cross-Model Convergent Analysis, and Summary. The WCST, GNG, and SST sections each include validity and reliability assessments, multivariate and univariate MANOVA analyses, and post hoc testing as appropriate. The Cook's Leverage-Residual Sensitivity Analysis section includes outlier detection results and comparative analysis of original versus refined models. The Cross-Model Convergent Analysis section presents framework comparison results and recommendations for optimal endophenotype combinations for AI feature engineering applications.

Data Collection

Data collection for the study occurred between April 8, 2024 and January 1, 2025 (268 days). As discussed in Chapter 3, participants were obtained from a U.S. sample of the Qualtrics pool of GenPop (general population) research panels comprising over 2.6 million members (as of February 2025). Qualtrics first matched the study's inclusion/exclusion criteria to its participating panel demographic self-report databases and solicited participants using the protocols described in Chapter 3. Participants first completed screening, informed consent, and demographic surveys in the Qualtrics gateway and then transferred to the Millisecond gateway to complete the self-report and laboratory behavioral measures. Participants who successfully completed the entire study (i.e., Qualtrics survey and BIS-11 plus of each of the three laboratory behavioral measures) transferred back to Qualtrics to log a completed (but unvalidated) study.

Figure 8 shows the progression of data collection to reach the final upper quartile (treatment) and lower quartile (control) groups of the BIS-11 Factor I motor impulsivity subscale for data analysis. To transfer from the Qualtrics gateway to the Millisecond gateway to complete the self-report and laboratory behavioral measures, participants were informed, prior to completing informed consent, that they would need to permit an auto-install of an executable software application on their computers (along with instructions on removing it post study). It is possible that resistance to, or failure of, this installation contributed to the low 54% overall transfer rate from the Qualtrics gateway to the Millisecond gateway. After about 60 days of data collection, 533 (9 per day) 18-34 yr old males had completed informed consent, 153 (2.6 per day; 29%) of those had completed the BIS-11 and 45 (0.76 per day; 8.4%) had completed the entire study (i.e., Qualtrics survey + valid [BIS-11 + GNG + SST + WCST]). At a yield of about eight percent and a requirement of 560-600 completed studies to sufficiently power the study, to generate upper and lower quartile groups, it was estimated that a total of 737 days (2 years) of data collection would be required. Consequently, the IRB approved (Appendix A) a request to change the demographic of the participants to include females (in addition to males) and 35-40 yr olds (in addition to 18-34 yr olds). These changes were consistent with literature data. The BIS-11 and other measures were normed in the literature against both biological sexes and broader age groups. Adding females and older participants would putatively also strengthen representation among the BPD and schizophrenia behavioral phenotypes. Consequently, pre-screening and demographic questions in the Qualtrics survey portion of the study were revised to enroll males and females ages 18-40. These changes significantly improved both enrollment and completion of the study after June 2024.

A total of 7,212 (27 per day) participants responded to the recruitment solicitation and attempted pre-screening questions over the 268 days of data collection. Of those, 6,603 (25 per day; $m = 4,109$, $f = 2,494$) completed informed consent and began the study by completing the demographic survey in the Qualtrics gateway. 3,566 (13 per day; 54%) of those completed the BIS-11 and 3,242 (12 per day; 49%) generated valid BIS-11 results. Following the BIS-11, as described in Chapter 3, the participants were presented with each of the three laboratory behavioral measures in random order. The SST had the lowest completion rate (42%) and also represented the lowest percentage (45%) of validated completions (percentage of completed SST's that passed validation criteria). The GNG had a completion rate of 43%, and 54% of those were valid. The WCST had a completion rate of 43%, and 84% of those were valid. A total of 1,101 (16.7% of the 6,603 study attempts) participants successfully completed the entire study (the Qualtrics survey and BIS-11 plus all three laboratory behavioral measures with valid results [through level one validation filters]). The average time for the 1,101 successful attempts to complete the entire study was 45 minutes (completion times for all four Millisecond instruments averaged 27.5 minutes with 98% of participants completing all four instruments in under 43 minutes). 954 (14.4% of the 6,603 study attempts) of the initial 1,100 participants who completed the entire study passed the final two levels of data validation filtering (before further statistical analysis for outliers). Matching groups of 240 participants for the upper quartile ($m = 150$, $f = 90$) and 240 participants for the lower quartile ($m = 134$, $f = 106$) were generated from this total to comprise the treatment (high BIS-11 Factor I motor impulsivity, FI-MI) and control groups (low BIS-11 Factor I motor impulsivity, FI-MI) for data analysis (the minimum required for a fully powered study was 140 participants per group).

Figure 8*Flow of Progression of Data Collection*

Data Pre-Processing

Qualtrics data collection statistics were checked, and Millisecond self-report and laboratory behavioral measure raw data was exported and screened once or twice per day over the 268-day data collection period. Summary data and raw data for each of the BIS-11, GNG, SST, and WCST were extracted from the Millisecond gateway data files and imported into distinct excel spreadsheets (one for each measure with a summary data tab and a raw data tab). Then, on a line-by-line basis, subject IDs (long strings of a combination of randomly generated letters and numbers) were manually matched from the BIS-11 to each of the three laboratory behavioral measures to identify and validate completed studies. Next, a first pass validation filtering step was conducted at least twice per week for each measure to identify valid results for full study matching to maximize data internal validity. First pass validation filtering included rejection of failed query parameters, failed tests, source platform study attempts from cellphone android and IOS operating systems despite requirements that study attempts required computers, error indicators, and BIS-11 overcontrol filters (multimodal holistic screening of BIS-11 totals below 52). For the SST, in addition to standard internal instrument validation filters, per Arnatkeviciute et al. (2023), data were rejected for any result that violated the racehorse model. If the racehorse model passed but pRs deviation = 1 and was not > 2 , results were rejected if z-scores were generally > 2 depending on holistic comparisons. SST results were also rejected if they had a stop accuracy rate lower than 25% or higher than 75% as reported in Millisecond summary data files (Arnatkeviciute et al., 2023) and any data sets with illogical task completion times (i.e., times exceed maximum possible sum of all task runs with no response, or values that were less than or greater than five standard deviations from the mean). For the GNG, in addition to standard internal instrument validation filters, data sets with a commission error rate of greater

than 0.8 or omission error rate of greater than 0.5 were rejected, per Deng et al. (2023). For the WCST, data were rejected that failed WCST internal standard validation criteria and criteria in the custom coding for this study (e.g., forced 128 card show). On a weekly basis, all demographic survey information in the Qualtrics gateway summary files were extracted and summarized, as were all descriptive statistics for each laboratory behavioral measure Millisecond data file. These summaries were reported to the dissertation committee chair on a weekly basis until the close of data collection.

Once data collection was closed and database lock occurred on January 1, 2025, each of the four individual excel spreadsheets of imported summary data for each of the BIS-11, GNG, SST, and WCST, were combined into a master excel spreadsheet for the BIS-11 and the three laboratory behavioral measures. The master set was sorted by subject IDs for each of the BIS-11 and three laboratory behavioral measures and then matched across all four measures manually, line-by-line. Next, all Qualtrics completed survey data were extracted from the .csv file structures and converted into tab delimited (.tsv) excel format to enable separation of multiple comorbidities or polypharmacy from the demographics data structures. Then, all 6,603 data sets were sorted by order of the subject ID as described above.

The 1,101 sorted subject IDs from the master Millisecond spreadsheet for the BIS-11 and three laboratory behavioral measures were then exported into the master spreadsheet with the Qualtrics survey data sets into a combined unmatched study master data set of 6,603 post informed consent participant arrays. The excel files for each of the four laboratory behavioral measures had randomly generated subject IDs (long strings of letters and numbers) for each participant. These subject IDs were transferred (as query parameters) from the Qualtrics data set for each participant upon transfer from the Qualtrics gateway to the Millisecond gateway so were

also included in the Qualtrics data set. This resulted in a total of seven subject ID groupings from the source data files. Consequently, the 1,101 imported subject IDs from the master spreadsheet for the four measures were compared manually line-by-line with the 6,603 sorted subject IDs for the Qualtrics data set (seven subject IDs for each participant) and reduced until only those participants with seven matching subject ID's remained for the combined data set, resulting in 1,101 final validated data sets (first pass of validation). Next followed several rounds of quality control and filtering to remove additional cases (participants) with questionable data (e.g., missing data fields, timing conflicts, etc.) and reconcile double (or triple or quadruple) subject ID conflicts (duplicate subject ID groupings were rejected using Qualtrics completion filters). The second pass reduced the data set to 996 (five participants [cases] removed) and the third pass reduced the data set to a final number of 954 (42 additional participants [cases] removed) valid Millisecond data sets for the Millisecond BIS-11 and three laboratory behavioral instruments matched to the Qualtrics surveys.

Once the final master data set was completed, it was sorted, first, by Factor I BIS-11 motor impulsivity scores from highest to lowest. The middle two quartiles were then removed from the data set (to ensure quality control and data integrity, every filtering step in data preprocessing resulted in a unique file before the next step) and the result was 240 upper quartile, and 240 lower quartile sets for a 480 participant total data size. G*Power required at least 280 (140 per group) for a fully powered study, but oversampling was necessary because data dropouts and statistical outliers could not be determined in advance.

Multiple level demographic and score descriptive statistics were calculated across the data set. To further maximize data internal validity, additional quality control on the subject IDs was conducted to ensure that multiple levels of sorting for demographics (e.g., scores by

biological sex, age, race, age, education, ADHD, ASD, Schizophrenia, BPD etc.) did not compromise data integrity. To confirm, a random number quality control sampling generating algorithm was developed and deployed to determine the number of random samples ($n = 215$) needed to test out of 480 total samples and to generate the random numbers (line items [cases] to be tested). All seven subject ID groups were matched for each random sample line item. The final Qualtrics validated master survey set of 6,603 was used for overall descriptive statistics of that data pool. The final master data set of 954 valid study completions was used for demographics of that data pool. The final master data file of BIS-11 Factor I motor impulsivity quartile score based 480 validated results (the study group) were used for descriptive statistics and MANOVA and post hoc analysis for hypothesis testing. A refined data set of 411 total cases (201 for the high FI-MI treatment group and 211 for the low FI-MI control group) following Cook's distance leverage-residual (influence) sensitivity analysis was used for exploratory MANOVAs following removal of influential outliers.

Study Demographics

Table 11 shows gender demographic statistics for study participants who completed the Qualtrics survey and for those who successfully completed the entire study (i.e., Qualtrics survey plus BIS-11 and each of the GNG, SST, and WCST with valid results). As data reduction progressed, the proportion of males to females remained generally consistent and the mean age and standard deviation remained constant. A total of 6,603 ($m = 62.2\%$, $f = 37.8\%$) participants completed the Qualtrics survey with a mean age of 31 ($SD = 6.3$). 954 of those who completed the Qualtrics survey successfully completed the entire study with valid results ($m = 59.2\%$, $f = 40.8\%$) with a mean age of 31 ($SD = 6.2$). The upper and lower quartiles of this group of 480 ($m = 59.2\%$, $f = 40.8\%$) also had a mean age of 31 ($SD = 6.2$). The upper quartile consisted of 150

males (62.5%) with a mean age of 32 and 90 females (37.5%) with a mean age of 31. The lower quartile consisted of 134 males (55.8%) with a mean age of 31 and 106 females (44.2%) with a mean age of 31.

Table 11

Gender Demographic Statistics of Study Participants

	<i>n</i>	<i>%</i>	Age ($\bar{x}$)	Age (<i>SD</i>)
Qualtrics survey completions				
Males	4,109	62.2	31.5	6.2
Female	2,494	37.8	31.1	6.4
Total	6,603		31.3	6.3
Completed studies (Qualtrics Survey + valid [BIS-11 + GNG + SST + WCST])				
Male	565	59.2	31.3	5.8
Female	389	40.8	30.4	6.7
Total	954		30.9	6.2
Upper + Lower quartiles of completed studies				
Male	284	59.2	31.5	
Female	196	40.8	31.0	
Total	480		31.2	6.2
Upper quartile (Treatment Group)				
Male	150	62.5	32.0	
Female	90	37.5	31.0	
Total	240		31.5	5.9

	<i>n</i>	%	Age ($\bar{x}$)	Age (<i>SD</i>)
Lower quartile (Control Group)				
Male	134	55.8	31.0	
Female	106	44.2	31.0	
Total	240		31.0	6.4

Note: Qualtrics survey collected broad demographic data. Instruments completed in the Millisecond Software gateway.

Table 12 shows race, ethnicity, and educational demographics for study participants who completed the Qualtrics survey, and those who successfully completed the entire study with valid results and comprised the final upper (treatment) and lower (control) quartile-based study group. 70.3% of the 6,603 participants who completed the Qualtrics study self-reported as white/Caucasian, 17.8% black/African American, and 5.2% Asian, with 5.5% self-reporting as other races or mixed and 1.2% preferring not to answer. This compares to the general U.S. population comprising 75.5% white/Caucasian, 13.7% black/African American, 6.4% Asian, and 4.4% mixed or other races (U.S. Census Bureau, 2020). 69.9% of the 480 upper and lower quartiles of those who successfully completed the entire study (the Study Group) self-reported as white/Caucasian, 18.1% as black/African American, 6.0% Asian, and 5.2% self-reporting as mixed or other races with 0.8% preferring not to answer. 18.6% of 6,603 Qualtrics survey participants and 16.9% of the 480 Study Group participants self-reported as Hispanic/Latino, compared to 19.5% Hispanic/Latino's in the U.S. population (U.S. Census Bureau, 2020). 97.3% of 6,603 Qualtrics study participants self-reported as high school graduates or higher and 58.7% as having a four-year degree or higher, compared to 89.4% and 35.0% respectively for the U.S.

population age 25 or over (U.S. Census Bureau, 2020). For the 480 Study Group participants 98.6% were high school graduates or higher and 52.1% had four-year college degrees or higher.

Table 12

Demographic Statistics of Study Participants

	Qualtrics Survey		Study Group	
	Participants			
	<i>n</i> = 6,603		<i>n</i> = 480	
	<i>n</i>	%	<i>n</i>	%
Race				
White/Caucasian	4,643	70.3	332	69.1
Black/African American	1,175	17.8	87	18.1
Asian	345	5.2	29	6.0
Native American	92	1.4	7	1.5
Pacific Islander	25	0.4	1	0.2
Mixed	247	3.7	20	4.2
Prefer not to answer	76	1.2	4	0.8
Ethnicity				
Hispanic/Latino	1,229	18.6	81	16.9
Mixed	207	3.1	14	2.9
Non-Hispanic/Latino	4,965	75.2	376	78.3
Prefer not to answer	202	3.1	9	1.9
Most education obtained				

	Qualtrics Survey		Study Group	
	Participants			
	<i>n</i> = 6,603		<i>n</i> = 480	
	<i>n</i>	%	<i>n</i>	%
Doctorate/professional degree	377	5.7	21	4.4
Masters	1,462	22.1	76	15.8
Four-year college degree	2,043	30.9	153	31.9
Some college	1,469	22.3	154	32.1
High school graduate	1,078	16.3	69	14.4
Some high school	107	1.6	5	1.0
Less than high school	39	0.6	1	0.2
Prefer not to answer	28	0.4	1	0.2

Note: Qualtrics Survey Participants = participants who signed informed consent and completed the Qualtrics survey and the BIS-11, without reference to whether they completed all three laboratory behavioral instruments; Study Group = participants (cases) used for primary study analysis (MANOVA models) and who completed entire study, passed all validation filters (*n* = 954) and then reduced to those from that group who represented the upper or lower quartile of Factor I motor impulsivity scores on the BIS-11.

Table 13 shows Qualtrics study participants (*n* = 6,603) with a self-reported DSM diagnosis of ADHD, ASD, schizophrenia, or borderline personality disorder (BPD) and certain self-reported comorbidities for each of those four behavioral phenotypes. 18.3% of participants self-reported an ADHD diagnosis (*m* = 62.3%, *f* = 37.7%) with a mean age of 31 (*SD* = 7.0),

compared with 6.0% ($m = 55.8\%$, $f = 44.2\%$) of the U.S. >18 adult population self-reporting an ADHD diagnosis (Staley et al., 2023) and prevalence rates of 2.5% - 15%. 7.4% of participants self-reported an ASD diagnosis ($m = 68.9\%$, $f = 31.1\%$) with a mean age of 31 ($SD = 7.0$), compared with a 2.2% prevalence rate in the U.S. adult population, which is not based on self-report data (IACC, 2023). 6.7% of participants self-reported a schizophrenia diagnosis ($m = 76.8\%$, $f = 23.2\%$) with a mean age of 33 ($SD = 6.0$), compared with 1.1% of Canadians who self-reported a schizophrenia diagnosis and U.S. prevalence rates of .7%-9% (American Psychiatric Association, 2022; Supina & Patten, 2006). 10.4% of participants self-reported a diagnosis of borderline personality disorder ($m = 64.9\%$, $f = 35.1\%$), compared with 6.4% of adults with BPD in primary care settings and 1.6% BPD prevalence in the general population (Mendez-Miller et al., 2022).

With respect to comorbidities, each of the four behavioral phenotypes was highly comorbid with the other. 22.1% of participants who self-reported a diagnosis of ADHD also self-reported ASD (compared with 14%-50% in the general ADHD population as noted in Chapter 3), with 16.8% self-reporting schizophrenia spectrum disorders (i.e., schizophrenia, schizophreniform disorder, schizoaffective disorder, and schizotypal personality disorder), and 10.4% self-reporting BPD. 55.4% of participants who self-reported a diagnosis of ASD also self-reported ADHD (compared with 28%-50% in the general ASD population as noted in Chapter 3), with 30.8% self-reporting schizophrenia spectrum disorders, and 34.5% self-reporting BPD. 43.0% of participants who self-reported schizophrenia also self-reported ADHD, 24.4% self-reported ASD, and 43% self-reported BPD. 46.7% of participants who self-reported BPD also self-reported ADHD, 24.3% self-reported ASD, and 32.9% self-reported schizophrenia spectrum disorders. ADHD was the most common comorbidity in participants who self-reported ASD,

schizophrenia, and BPD. Anxiety disorder was the most common comorbidity of those who self-reported a diagnosis of ADHD (44.7%), second most common for ASD (41.5%) and BPD (44.9%), and third most common for schizophrenia (38.8%). Two additional comorbidities were relatively consistently self-reported across all four behavioral phenotypes, major depressive disorder (24.1% - 27.7%) and PTSD (20.8% - 24.6%).

Table 13

DSM Demographics from Qualtrics Survey

	Total	ADHD	ASD	Schizo	BPD
<i>n</i>	6,603	1,212	487	307	690
% of total with diagnosis	52.9	18.3	7.4	6.7	10.4
Males (%)	62.2	62.3	68.9	76.8	64.9
Females (%)	37.8	37.7	31.1	23.2	35.1
Age ($\bar{x}$)	31.3	31.0	31.0	33.0	33.0
Age (<i>SD</i>)	6.3	7.0	7.0	6.0	6.0
Comorbidities (% of Tot/Disorder)					
ADHD	18.3		55.4	43.0	46.7
Autism Spectrum Disorder	7.4	22.1		24.4	24.3
Schizophrenia Spectrum	16.8	10.2	30.8		32.9
BPD	10.4	18.5	34.5	43.0	
Anxiety Disorder	26.7	44.7	41.5	38.8	44.9
Major Depressive Disorder	10.5	24.1	27.7	25.7	27.1
Bipolar Disorder	9.2	16.7	20.7	34.2	28.6

	Total	ADHD	ASD	Schizo	BPD
OCD	6.2	14.4	18.1	18.2	18.7
PTSD	8.6	20.9	24.6	20.8	22.6
Addictive Disorders	11.5	18.2	19.5	28.7	27.5

Note: DSM self-report diagnosis shown only for the four behavioral phenotypes of this study.

For comorbidities, not all comorbidities are shown; Schizophrenia spectrum = schizophrenia, schizophreniform disorder, schizoaffective disorder, and schizotypal personality disorder.

Addictive disorders = substance use disorder + alcoholism.

Table 14 shows BIS-11 total scores (the sum of all six Factor II scores or sum of 3 Factor I scores) for study participants who completed the Qualtrics survey and had valid results for the BIS-11 and three laboratory behavioral measures, by gender, the four behavioral phenotypes, participants who self-reported as having no DSM diagnosis (neurotypicals), and population norms reported by Patton et al. (1995). The table shows means, standard deviations, theoretical upper and lower quartiles and actual upper and lower quartile total score cutoffs and quartile means. The maximum range of BIS-11 total scores is 30 – 120 with the study participants ranging from 35 – 111. Normal levels of impulsivity as measured by BIS-11 total scores reported by Patton et al. (1995) range from 51 – 71, $\bar{x} = 62$, $SD = 11$, $n = 1,577$, with 72 (or > 80th percentile) or higher considered impulsive (Coutlee et al., 2014; Stanford et al., 2009) and a score of 95 representing the 99.9th percentile (three standard deviations above the mean). Neurotypical study participants ($n = 433$, 45.4% of total) had a mean BIS-11 total score of 61 ($SD = 12$), consistent with the normed sample by Patton et al. (1995).

Study participants who self-reported being diagnosed with ADHD ($n = 200$) had a mean BIS-11 total score of 74 (86th percentile of norms), ASD ($n = 59$) 72 (82nd percentile), and BPD ($n = 46$) 74 (86th percentile), each with a standard deviation of 11, and schizophrenia ($n = 18$) 75 (88th percentile) with a standard deviation of 14, all in the impulsive range. For all study participants (neurotypicals plus self-reported DSM diagnosis) who completed the Qualtrics survey, BIS-11 and all three laboratory behavioral measures ($n = 954$) mean BIS-11 total score was 66 ($SD = 12.7$) with participants who self-reported at least one DSM diagnosis ($n = 521$, 54.6% of total) having a mean score of 69 (74th percentile of norms). Male participants ($n = 565$) had a mean score of 65 ($SD = 13$) and female participants 67 ($SD = 13$).

The actual cut-off score for the upper quartile of study participants (cases) was 75 (88th percentile of norms) and lower quartile cut-off was 56 (29th percentile), each of which was identical to their theoretical values. The mean BIS-11 total impulsivity score for the upper quartile of study participants was 82 (97th percentile of norms) with a standard deviation of 6 and the bottom quartile had a mean score of 50 (14th percentile) with a standard deviation of 5 (note that the upper and lower quartile participants based on BIS-11 total scores do not comprise the study group because the quartiles that comprise the study group are based on Factor I BIS-11 scores for motor impulsivity (MI) so some participants that are in the quartiles for total scores may not be in the upper and lower quartiles based on Factor I MI scores).

Table 14*BIS-11 Total Scores for Completed Studies*

	Norm	Total	Males	Females	Neurotyp	ADHD	ASD	Schizo	BPD
	<i>n</i> =1,577	<i>n</i> =954	<i>n</i> =565	<i>n</i> =389	<i>n</i> =433	<i>n</i> =200	<i>n</i> =59	<i>n</i> =18	<i>n</i> =46
$\bar{x}$	62	66	65	67	61	74	72	75	74
<i>SD</i>	11	12.7	13	13	12	11	11	14	11
<i>T-UQ</i>	70	75	75	77	69	82	80	86	82
<i>UQ</i>		75	74	75	68	81	81	87	83
<i>UQ-$\bar{x}$</i>		82							
<i>T-LQ</i>	55	56	55	57	52	66	64	65	66
<i>LQ</i>		56	55	57	52	67	67	65	67
<i>LQ-$\bar{x}$</i>		50							

Note: Completed studies = Qualtrics survey + valid (BIS-11 + GNG + SST + WCST). Norm = instrument norms reported by Patton et al. (1995); 51-71 represent healthy levels of impulsivity (Stanford et al., 2009). Total = sum of three Factor II motor impulsivity scores from this study. *UQ/LQ* = Upper Quartile/Lower Quartile. Theoretical quartiles (*T-UQ/T-LQ*) calculated at $\pm 67.4\%$ of *SD* used as a rough initial standard of normality. *UQ- $\bar{x}$ /LQ- $\bar{x}$* = means for upper and lower quartiles. Neurotyp(ical) = participants with no self-reported DSM diagnosis.

Table 15 shows BIS-11 Factor I motor impulsivity scores for study participants who completed the Qualtrics survey and had valid results for the BIS-11 and three laboratory behavioral measures, by gender, the four behavioral phenotypes, and participants who self-reported as having no DSM diagnosis (neurotypicals). The table shows means, standard

deviations, theoretical upper and lower quartiles and actual upper and lower quartile total score cutoffs and quartile means. The maximum range of BIS-11 Factor I motor impulsivity scores is 7 - 28 with the study participants also ranging from 7 – 28. Theoretical baseline Factor I motor impulsivity BIS-11 score from Chapter 3 is a mean of 15 ($SD = 3$). Neurotypical study participants ($n = 433$, 45.4% of total) had a mean Factor I motor impulsivity score of 15 ($SD = 4$).

Study participants who self-reported being diagnosed with ADHD ($n = 200$) had a mean Factor I motor impulsivity score of 17 (75th percentile of theoretical baseline from Chapter 3), ASD ($n = 59$) 17 (75th percentile), and BPD ($n = 46$) 18 (77th percentile), each with a standard deviation of 4, and schizophrenia ($n = 18$) 19 (91st percentile) with a standard deviation of 5. For all study participants (neurotypicals plus self-reported DSM diagnosis) who completed the Qualtrics survey, BIS-11 and all three laboratory behavioral measures ($n = 954$), mean BIS-11 Factor I motor impulsivity score was 16 ($SD = 4$; 63rd percentile of theoretical baseline) with participants who self-reported at least one DSM diagnosis ($n = 521$, 54.6% of total) having a mean score of 16.8 (73rd percentile of theoretical baseline from Chapter 3). Male participants ($n = 565$) had a mean score of 16 ($SD = 4$) and female participants also 16 ($SD = 4$). The cut-off score for the upper quartile of study participants was 18 (77th percentile of theoretical baseline from Chapter 3) and lower quartile cut-off was 13 (25th percentile), very close to their theoretical values. The mean BIS-11 Factor I motor impulsivity score for the upper quartile of study participants was 21 (98th percentile) with a standard deviation of 2 and the bottom quartile had a mean score of 11 (9th percentile) with a standard deviation of 1.

Table 15*BIS-11 Factor I Motor Impulsivity Scores for Completed Studies*

	Total	Males	Females	Neurotyp	ADHD	ASD	Schizo	BPD
	<i>n</i> =954	<i>n</i> =565	<i>n</i> =389	<i>n</i> =433	<i>n</i> =200	<i>n</i> =59	<i>n</i> =18	<i>n</i> =46
$\bar{x}$	16	16	16	15	17	17	19	18
<i>SD</i>	4	4	4	4	4	4	5	4
<i>T-UQ</i>	19	19	19	18	20	20	23	21
<i>UQ</i>	18	19	18	17	19	19	23	22
<i>UQ-$\bar{x}$</i>	21							
<i>T-LQ</i>	13	13	13	12	14	14	15	15
<i>LQ</i>	13	13	13	13	14	14	16	15
<i>LQ-$\bar{x}$</i>	11							

Note: Completed studies = Qualtrics survey + valid (BIS-11 + GNG + SST + WCST). UQ/LQ = Upper Quartile/Lower Quartile. Theoretical quartiles (*T-UQ/T-LQ*) calculated at $\pm 67.4\%$ of SD used as a rough initial standard of normality. *UQ- $\bar{x}$ /LQ- $\bar{x}$* = means for upper and lower quartiles. Neurotyp(ical) = participants with no self-reported DSM diagnosis.

Table 16 shows BIS-11 Factor II motor impulsivity scores for study participants who completed the Qualtrics survey and had valid results for the BIS-11 and three laboratory behavioral measures, by gender, the four behavioral phenotypes, and participants who self-reported as having no DSM diagnosis (neurotypicals). The table shows means, standard deviations, theoretical upper and lower quartiles and actual upper and lower quartile total score

cutoffs and quartile means. The maximum range of BIS-11 Factor II motor impulsivity scores is 11 – 44 with the study participants ranging from 12 – 41. Theoretical baseline of Factor II motor impulsivity BIS-11 score from Chapter 3 is a mean of 22.5 ($SD = 3.7$). Neurotypical study participants ($n = 433$, 45.4% of total) had a mean Factor II motor impulsivity score of 22 ($SD = 5$). Study participants who self-reported being diagnosed with ADHD ($n = 200$) had a mean Factor II motor impulsivity score of 29 ($SD = 5$; 96th percentile of theoretical baseline from Chapter 3), ASD ($n = 59$) 26 ($SD = 6$; 83rd percentile), schizophrenia ($n = 18$) 29 ($SD = 7$; 96th percentile), and BPD ($n = 46$) 27 ($SD = 6$; 89th percentile). For all study participants (neurotypicals plus self-reported DSM diagnosis) who completed the Qualtrics survey, BIS-11 and all three laboratory behavioral measures ($n = 954$) mean BIS-11 Factor II motor impulsivity score was 24 ($SD = 5$) with participants who self-reported at least one DSM diagnosis ($n = 521$, 54.6% of total) having a mean score of 25.7 (81st percentile of theoretical baseline from Chapter 3). Male participants ($n = 565$) had a mean score of 24 ($SD = 5$) and female participants ($n = 389$) a mean score of 23 ($SD = 5$).

The cut-off score for the upper quartile of study participants was 27 (89th percentile of theoretical baseline from Chapter 3) and lower quartile cut-off was 20 (25th percentile), the same as their theoretical values. The mean BIS-11 Factor II motor impulsivity score for the upper quartile of study participants was 30 (98th percentile) with a standard deviation of 3 and the bottom quartile had a mean score of 18 (11th percentile) with a standard deviation of 2.

Table 16*BIS-11 Factor II Motor Impulsivity Scores for Completed Studies*

	Total	Males	Females	Neurotyp	ADHD	ASD	Schizo	BPD
	<i>n</i> =954	<i>n</i> =565	<i>n</i> =389	<i>n</i> =433	<i>n</i> =200	<i>n</i> =59	<i>n</i> =18	<i>n</i> =46
$\bar{x}$	24	24	23	22	29	26	29	27
<i>SD</i>	5	5	5	5	5	6	7	6
<i>T-UQ</i>	27	28	27	26	29	31	34	32
<i>UQ</i>	27	27	26	25	28	28	34	32
<i>UQ-$\bar{x}$</i>	30							
<i>T-LQ</i>	20	20	19	18	21	22	24	23
<i>LQ</i>	20	20	20	19	22	22	24	23
<i>LQ-$\bar{x}$</i>	18							

Note: Factor II motor impulsivity score = sum of Factor I Motor impulsivity and Factor I perseverance (Patton et al., 1995). Factor I *UQ/LQ* = Upper Quartile/Lower Quartile. Theoretical quartiles (*T-UQ/T-LQ*) calculated at $\pm 67.4\%$ of SD used as a rough initial standard of normality. *UQ- $\bar{x}$ /LQ- $\bar{x}$* = means for upper and lower quartiles. Neurotyp(ical) = participants with no self-reported DSM diagnosis.

Table 17 shows three factor scores for the BIS-11, GNG, SST, and WCST for all study participants (cases) who completed the Qualtrics survey and all four Millisecond instruments successfully with fully validated results ($n = 954$), neurotypicals ($n = 433$; participants who self-reported no DSM diagnosis), ADHD ($n = 200$), ASD ($n = 59$), schizophrenia ($n = 18$), and BPD

($n = 46$). These values are provided to enable face comparison to values for the quartiles of the Study Group below.

Table 17

BIS-11, GNG, SST, WCST Mean Scores for Completed Studies

	<i>n</i>	BIS-11			GNG			SST			WCST		
		Tot	FII	FI	mRt	CE	OE	SSRT	CE	OE	PR	NPE	FMS
NTyp	433	61	22	15	359	6	10	277	27	10	22	18	1
Total	954	66	24	16	352	7	9	281	27	9	22	19	1
ADHD	200	74	25	17	334	8	7	275	28	7	21	19	2
ASD	59	72	26	17	340	10	8	308	29	9	21	19	2
Schiz	18	75	29	19	407	11	17	471	29	17	19	18	2
BPD	46	74	27	18	362	8	14	332	28	12	24	20	1

Note: NTyp = neurotypical (no self-report DSM diagnosis); GNG: mRt = mean reaction time in milliseconds, CE = commission errors, OE = omission errors; SST: SSRT = stop signal reaction time in milliseconds; WCST: PR = preservative responses, NPE = non-preservative errors, FMS = failure to maintain set.

Study Group Data

Table 18 shows three factor scores for the BIS-11, GNG, SST, and WCST for all study participants who completed the Qualtrics survey and all four Millisecond instruments successfully with fully validated results ($n = 954$) for the upper and lower quartile groups ($n = 480$) based on BIS-11 Factor I motor impulsivity subscale scores (the Study Group). The mean FI motor impulsivity score of the upper quartile was 21, $SD = 2.2$, range = 18-28, and the mean

FI motor impulsivity score for the lower quartile was 11, $SD = 1.5$, range = 7-13. By comparison, these FI quartiles had mean BIS-11 total scores of 77, $SD = 10$, range = 46 – 111, for the upper quartile and 54, $SD = 9$, range = 35-77, for the lower quartile, and mean FII motor impulsivity subscale scores of 30, $SD = 3.4$, range = 23-41, for the upper quartile and 18, $SD = 2.3$, range = 12-25, for the lower quartile.

Table 18

BIS-11, GNG, SST, WCST Mean Scores for Study Group by BIS-11 Factor I MI Quartiles

	BIS-11			GNG			SST			WCST		
	Tot	FII	FI	mRt	CE	OE	SSRT	CE	OE	PR	NPE	FMS
<i>UQ (Treatment)</i>												
$\bar{x}$	77	30	21	359	8	12	307	28	11	23	21	2
SD	10	3.4	2.2	98	9	24	202	5	18	12	14	1
Max	111	41	28	840	40	198	1162	42	104	59	84	7
Min	46	23	18	124	0	90	74	17	0	6	3	0
<i>LQ (Control)</i>												
$\bar{x}$	54	18	11	353	6	9	269	27	9	23	18	1
SD	9	2.3	1.5	93	7	21	174	4	18	15	10	1
Max	77	25	13	936	41	128	1124	41	117	98	77	5
Min	35	12	7	132	0	0	39	18	0	4	4	0

Note: Based on upper and lower quartiles of BIS-11 Factor I motor impulsivity subscale scores;

GNG: mRt = mean reaction time in milliseconds, CE = commission errors, OE = omission

errors; SST: SSRT = stop signal reaction time in milliseconds; WCST: PR = preservative

responses, NPE = non-preservative errors, FMS = failure to maintain set.

Validity and Reliability of the Data Generally

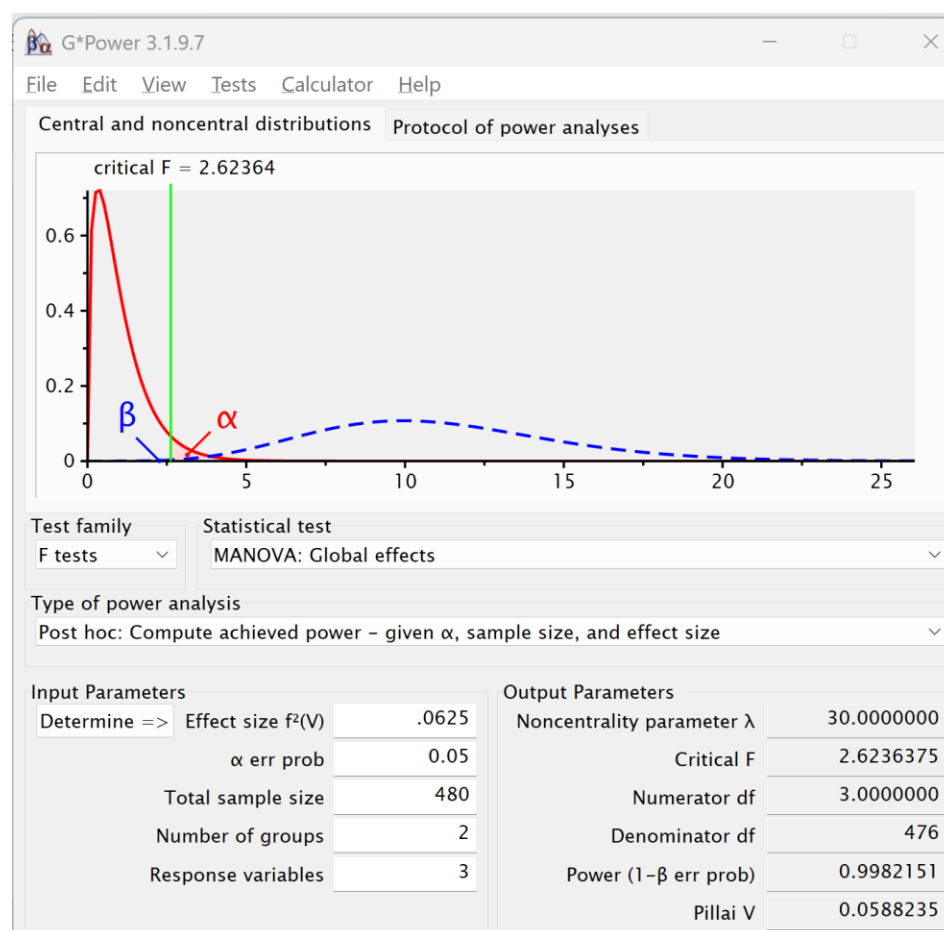
Multivariate analysis of variance (MANOVA) is a component of the general linear model (GLM) and, as such, is subject to nine primary assumptions: continuous quantitative dependent variables, at least two independent variables that are categorical or group variables, independence of observations, sample size sufficient for statistical power, multivariate normality, no univariate or multivariate outliers, linearity for each pair of dependent variables in each independent variable group, homogeneity of variance-covariance matrices, and absence of multicollinearity (Kraska, 2022). The dependent variables for all three studies (research questions/hypothesis), as scale numeric continuous values, meet the continuity assumption, and the independent variables, of high (treatment) and low (control) BIS-11 Factor I motor impulsivity, are categorical and, consequently, meet that assumption. Further, because each case (participant/case) belongs to one unique group (high or low) there exists independence of observations such that the assumption is met. This condition was tested and validated above with removal of Subject ID duplicates described above after robust comparisons.

Further, the sample size of 480 is far more than sufficient and well above the number of dependent variables (71% more than required for a fully powered study) and the sample size suggested by G*Power in Chapter 3 ($n = 280$). Figure 9 shows a G*Power post hoc analysis of the study showing an actual power of .998, indicating an overpowered study. This means there was a 99.8% probability of correctly detecting an effect if one truly existed (if there was a meaningful difference between high and low FI-MI groups) at the observed effect size or larger, which far exceeds the conventional 80% standard in the literature (Cohen, 1988). Thus, there was a 0.2% chance of Type II errors (missing a genuine effect) for this study, rather than the standard 20%, resulting in 100-fold reduction (improvement) in Type II error risk. Consequently,

the study design and power (a) support high confidence that the findings are genuine, (b) validates the influence sensitivity analysis in that removed influential outliers were genuinely problematic (discrepant), (c) make the findings (results) easier to replicate. As stated in Chapter 3, many literature studies are too underpowered to detect genuine effects or enable replicable findings.

Figure 9

*G*Power Analysis of Actual Power of Completed Study*



Research Question 1 (RQ1) H1, The Wisconsin Card Sorting Test (WCST)

RQ1 (Adjusted for revised sample population)

Do linear variates of perseverative responses (PR), non-perseverative errors (NPE), and failure to maintain set (FMS) measures on the Wisconsin Card Sorting test (WCST) differ between high and low motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults ages 18-40?

RQ1a. Is there a difference in perseverative responses (PR) in the WCST between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40?

RQ1b. Is there a difference in non-perseverative errors (NPE) in the WCST between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40?

RQ1c. Is there a difference in failure to maintain set (FMS) measures in the WCST between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40?

H1₀ (Null Hypothesis, Adjusted for Revised Sample Population)

Linear variates of perseverative responses (PR), non-perseverative errors (NPE), and failure to main set (FMS) measures on the Wisconsin Card Sorting Test (WCST) do not differ between high and low motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults ages 18-40.

H1_a (Alternate Hypothesis, Adjusted for Revised Sample Population)

Linear variates of perseverative responses (PR), non-perseverative errors (NPE), and failure to main set (FMS) measures on the Wisconsin Card Sorting test (WCST) differ between high and low motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults 18-40.

H1a0. There is no difference in perseverative responses (PR) in the WCST between high and low motor impulsiveness subscale groups on the BIS-11 in adults 18-40.

H1aA. There is a difference in perseverative responses (PR) in the WCST between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H1b0. There is no difference in non-perseverative errors (NPE) in the WCST between high and low motor impulsiveness subscale groups on the BIS-11 in adults 18-40.

H1bA. There is a difference in non-perseverative errors (NPE) in the WCST between high and low motor impulsiveness subscale groups on the BIS-11 in adults 18-40.

H1c0. There is no difference in failure to maintain set (FMS) measures in the WCST between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H1cA. There is a difference in failure to maintain set (FMS) measures in the WCST between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

Validity and Reliability of the Data: Hypothesis 1 (RQ1): WCST Model

The WCST model demonstrated psychometric soundness consistent with the established literature reviewed in Chapter 3 for the instrument. The three-factor structure identified through PCA, EFA, and CFA discussed in Chapter 3 was supported by the current study's data, with perseverative responses (PE) and non-perseverative errors (NPE) showing the expected moderate positive correlation ($r = .351$). The significant effect of NPE on BIS-11 Factor I motor impulsivity aligns with previous findings that factor II (non-perseverative errors; NPE) of the loading factors for the WCST reported by Greve et al., 1997 and Greve et al., 2005 is associated with aggressive impulsivity and inhibition. The WCST instrument's ability to discriminate motor impulsivity groups supports its continued use as a valid measure of prefrontal cortical function and executive control.

Table 19 shows the tests for normality for the WCST model (RQ1/Hypothesis 1). Considering the sample size (>50) the results of a Kolmogorov-Smirnov test were used to evaluate normality rather than the Shapiro-Wilk test, which is better for small sample sizes. None of the three dependent (outcome) variables for RQ1 Hypothesis 1 (WCST) were normally distributed, $p < .001$, by this measure. Due to the central limit theorem, large sample size, and equal group sizes, however, MANOVA is generally robust to normality violations.

Table 19

Tests for Normality for the WCST Model

		Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Group	Statistic	df	p	Statistic	df	p
PR	1	.167	240	<.001	.811	240	<.001
	2	.122	240	<.001	.924	240	<.001
NPE	1	.145	240	<.001	.822	240	<.001
	2	.191	240	<.001	.803	240	<.001
FMS	1	.200	240	<.001	.869	240	<.001
	2	.204	240	<.001	.872	240	<.001

Note: 1 = control group, 2 = treatment group. PR = perseverative responses, NPE = non-perseverative errors, FMS = failure to maintain set.

^a Lilliefors Significance Correction.

Table 20 shows descriptive statistics for the WCST perseverative responses (PR) dependent (outcome) variable for each of the high (treatment) and low (control) BIS-11 Factor I motor impulsivity (FI-MI) groups. If tests for normality do not pass, skewness and kurtosis at or

close to zero may indicate oversensitivity of normality tests due to a large sample size. Skewness for PR was moderately positive (right tailed) for the low FI-MI - control (skewness = 2.039) and modestly positive for the high FI-MI treatment (skewness = 0.888) groups. Kurtosis was high for control group (kurtosis = 5.452), but close to normal for the treatment group (kurtosis = 0.174). Mean for PR was slightly lower for the high FI-MI treatment group, $\bar{x} = 22.57$ [95% CI: 21.98, 24.05], than the low FI-MI control group, $\bar{x} = 22.98$ [95% CI: 21.09, 24.90]. PR for the control group (low FI-MI) was more variable, $SD = 14.93$, $s^2 = 222.85$, than that for the treatment (high FI-MI) group, $SD = 11.63$, $s^2 = 135.36$. Overall, there was a minimal difference between groups on PR.

Table 20

Descriptive Statistics for PR for the WCST Model

		Control (Low FIMI)		Treatment (High FIMI)	
		Statistic	SE	Statistic	SE
PR					
	($\bar{x}$)	22.98	.964	22.57	.751
95% Confidence Interval for	Upper Bound	21.09		21.09	
Mean	Lower Bound	24.88		24.05	
5% Trimmed Mean		21.38		21.79	
Median (<i>Mdn</i>)		18.00		20.00	
Variance (s^2)		222.85		135.36	
Std. Deviation (<i>SD</i>)		14.93		11.63	
Minimum		4.00		6.00	

	Control (Low FIMI)		Treatment (High FIMI)	
	Statistic	SE	Statistic	SE
Maximum	98.00		59.00	
Range	94.00		53.00	
Interquartile Range (<i>IQR</i>)	14.75		17.75	
Skewness	2.039	.157	0.888	.157
Kurtosis	5.452	.313	0.174	.313

Note: PR = preservative responses.

Table 21 shows descriptive statistics for the WCST non-perseverative errors (NPE) dependent (outcome) variable for each of the low (control) and high (treatment) BIS-11 Factor I motor impulsivity groups. Skewness for NPE was slightly higher for the control (skewness = 2.183) than treatment (skewness = 1.869) groups, indicating a moderately positive distribution. Kurtosis was very high for the control group (kurtosis = 7.327) and high for the treatment group (kurtosis = 3.863). Mean for the treatment (high FI-MI) group, $\bar{x} = 18.03$ [95% CI: 16.75, 19.31], was slightly lower than the mean for the control (low FI-MI) group, $\bar{x} = 20.88$ [95% CI: 19.11, 22.65]. The confidence intervals had minimal overlap, suggesting significant differences between groups. However, NPE for the treatment group (high FI-MI) was more almost twice as variable, $SD = 13.92$, $s^2 = 193.8$, than that for the control (low FI-MI) group, $SD = 10.08$, $s^2 = 101.58$, which may violate homogeneity assumptions. Overall, NPE was more indicative of group differences than PR.

Table 21*Descriptive Statistics of NPE for the WCST Model*

	Control (Low FIMI)		Treatment (High FIMI)	
	Statistic	<i>SE</i>	Statistic	<i>SE</i>
NPE				
$\bar{x}$	18.03	.6518	20.88	.899
95% Confidence Interval for $\bar{x}$	16.75		19.11	
5% Trimmed Mean	16.94		19.31	
Median (<i>Mdn</i>)	15.00		16.00	
Variance (s^2)	101.58		193.80	
Std. Deviation (<i>SD</i>)	10.08		13.92	
Minimum	4.00		3.00	
Maximum	77.00		84.00	
Range	73.00		81.00	
Interquartile Range (<i>IQR</i>)	11.00		13.75	
Skewness	2.183	.157	1.869	.157
Kurtosis	7.327	.313	3.863	.313

Note: NPE = non-perseverative errors.

Table 22 shows descriptive statistics for the WCST failure to maintain set (FMS) dependent (outcome) variable for each of the low (control) and high (treatment) BIS-11 Factor I motor impulsivity groups. Skewness for FMS was slightly lower for the control (skewness = 0.810) than treatment (skewness = 0.970) groups, indicating a moderately positive distribution. Kurtosis was for the control group (kurtosis = 0.170) was near normal and slightly high for the treatment group (kurtosis = 0.733). Mean for the treatment (high FI-MI) group, $\bar{x} = 1.50$ [95% CI: 1.32, 1.69], was slightly lower than the mean for the control (low FI-MI) group, $\bar{x} = 1.50$ [95% CI: 1.32, 1.69]. The confidence intervals significantly overlapped, suggesting a small effect size. Variability for FMS for the treatment (high FI-MI) group, $SD = 1.43$, $s^2 = 2.050$, and control (low FI-MI) group, $SD = 1.25$, $s^2 = 1.561$, with a variance ratio of 1.3:1, suggested the treatment group was more variable than the control group.

Table 22

Descriptive Statistics of FMS for the WCST Model

		Control (Low FIMI)		Treatment (High FIMI)	
		Statistic	SE	Statistic	SE
FMS					
$\bar{x}$		1.33	.081	1.50	.092
95% Confidence Interval for	Upper Bound	1.17		1.32	
Mean	Lower Bound	1.49		1.69	
5% Trimmed Mean		1.23		1.39	
Median (<i>Mdn</i>)		1.00		1.00	
Variance (s^2)		1.56		2.05	

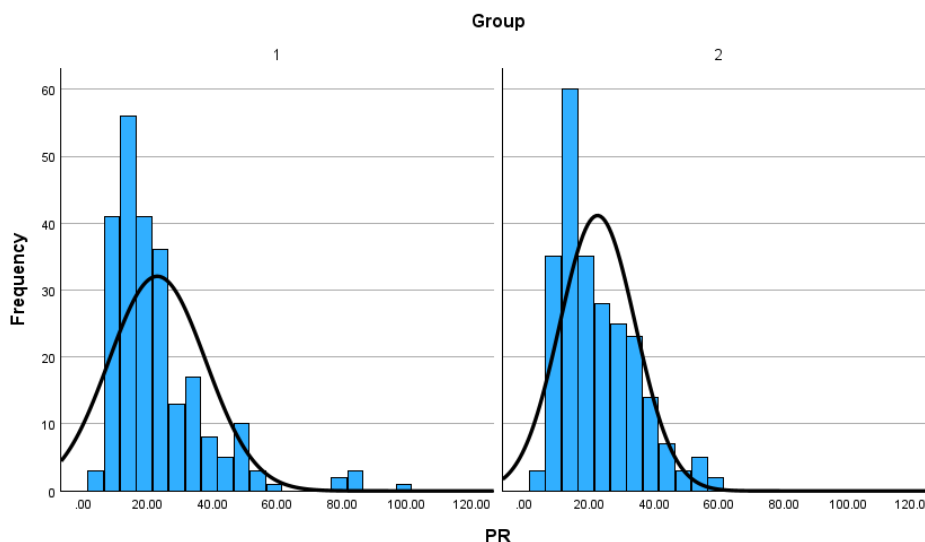
	Control (Low FIMI)		Treatment (High FIMI)	
	Statistic	SE	Statistic	SE
Std. Deviation (<i>SD</i>)	1.25		1.43	
Minimum	0.00		0.00	
Maximum	5.00		7.00	
Range	5.00		7.00	
Interquartile Range (<i>IQR</i>)	2.00		2.00	
Skewness	0.810	.157	0.970	.157
Kurtosis	0.170	.313	0.733	.313

Note: FMS = failure to maintain set.

Histograms were run in SPSS to also test the normality assumption and boxplots and scatter plots for linearity and univariate outliers for the WCST model. Significant multivariate outliers were identified using Mahalanobis distance and Cook's distance. Histograms were run on all three dependent (outcome) variables. Generally, all frequency distributions of the dependent (outcome) variables did not meet normality assumptions. Figure 10 visually shows the results of histogram for the test of the linearity assumption for the treatment group (high FI-MI) and the control group (low FI-MI) for PR. The distributions were uniformly positively skewed as confirmed by the descriptive statistics shown at Table 20. While there are slight differences between groups, distributions were generally similar.

Figure 10

Histogram of PR Distribution for Treatment Group for the WCST Model

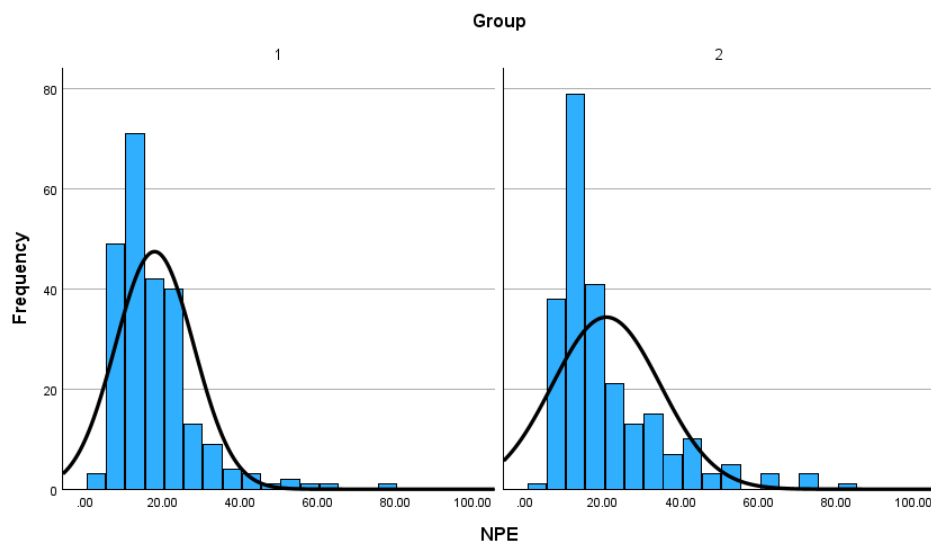


Note: PR = preservative responses.

Figure 11 visually shows the results of histogram for the test of the linearity assumption for the treatment group (high FI-MI) and the control group (low FI-MI) for NPE. The distributions were uniformly positively skewed as confirmed by the descriptive statistics shown at Table 21. Unlike PR, distributions are distinct with the treatment (high FI-MI) demonstrating higher NPE values with a longer positive tail as a group, confirming previous findings and suggestion of possible statistical significance.

Figure 11

Histogram of NPE Distribution for Treatment Group for the WCST Model

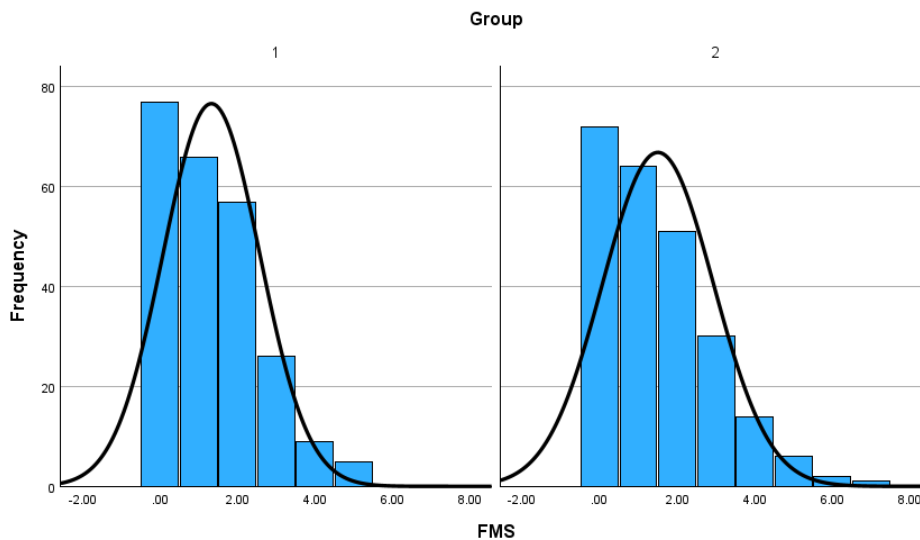


Note: NPE = non-preservative errors.

Figure 12 visually shows the results of histogram for the test of the linearity assumption for the treatment group (high FI-MI) and the control group (low FI-MI) for FMS. The distributions were uniformly positively skewed as confirmed by the descriptive statistics shown at Table 22. Although there are slightly more significant differences between groups than for PR (slight rightward shift for the treatment group [high F1-MI]), distributions were substantially overlapping and generally similar.

Figure 12

Histogram of FMS Distribution for Treatment Group for the WCST Model



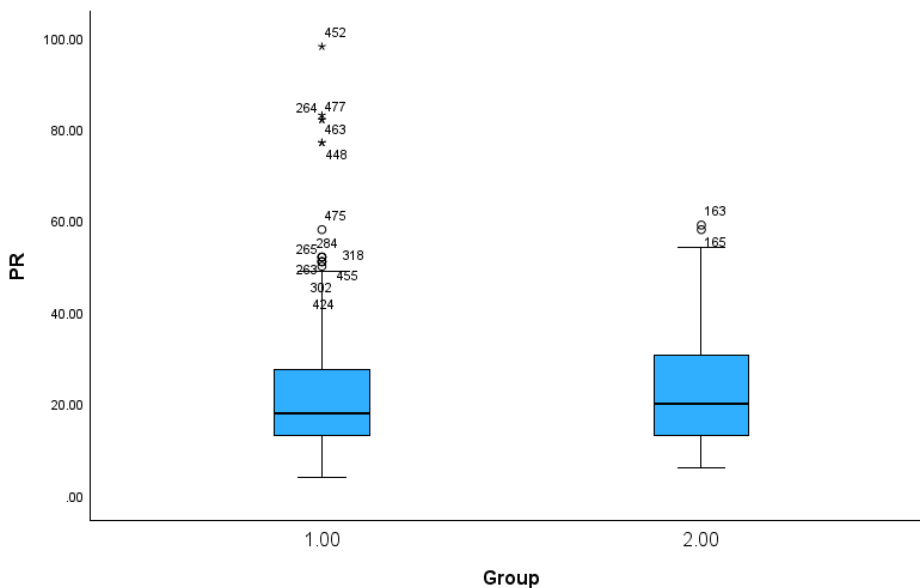
Note: FMS = failure to maintain set.

With respect to univariate outliers, Figure 13 shows Boxplots for both the treatment (high BIS-11 Factor I motor impulsivity) and control (low) groups for PR for the WCST model. The box for the treatment group (high FI-MI, Group 2 in Figure 7) shows slightly higher variability in the interquartile range (*IQR*; middle 50%) of PR values than the box for the control group (low FI-MI, Group 1 in Figure 13). The median line for the treatment group (Group 2) shows a thicker box above the median line than that of the control group (Group 1). Whiskers ($1.5 \times IQR$) also show slightly greater variability for the treatment (high) group than the control (low) group. However, to the extent there are differences between groups, those differences appear to be driven by a higher number of outliers (at a 6.5:1 ratio) in the control group versus the treatment group, rather than due to systematic group differences. The control group had only two positive outliers ($1.5 - 3 \times IQR$), and no extreme positive outliers ($>3 \times IQR$), while the

treatment group had eight positive outliers and five extreme positive outliers. The total outliers of the control (low) control group comprised 5.4% of cases (participants) while the total outliers of the treatment (high) control group comprised less than 1% of cases. Counterintuitively, a significant number of participants from the low BIS-11 Factor I motor impulsivity group demonstrated high preservative responding (PR) on the WCST while an insignificant number from the high FI-MI group did.

Figure 13

Boxplots of PR for Treatment and Control Groups for the WCST Model



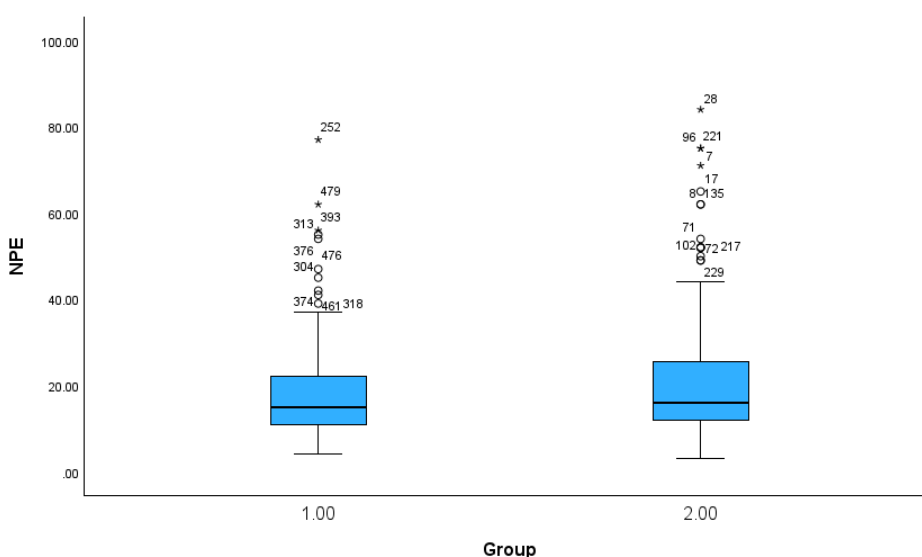
Note: PR = perseverative responses

Figure 14 shows Boxplots for both the treatment (high BIS-11 Factor I motor impulsivity) and control (low) groups for NPE for the WCST model. The box for the control group (low FI-MI, Group 1 in Figure 14) has less variability and less positive skew in the interquartile range (*IQR*; middle 50%) of NPE values for the WCST than the treatment group

(high FI-MI, Group 2 in Figure 14). Whiskers ($1.5 \times IQR$) also show greater variability and positive skew for the treatment (high) group than the control (low) group. The control group had six positive outliers ($1.5 - 3 \times IQR$) and three extreme outliers (no negative outliers). The treatment group had 11 positive outliers and four extreme outliers (no negative outliers). The outliers of the control (low) control group comprised 3.8% of cases (participants). The outliers of the treatment (high) control group comprised 6.3% of cases. Compared to PR, group differences do appear systematic and more significant with clear box separation, confirming earlier results.

Figure 14

Boxplots of NPE for Treatment and Control Groups for the WCST Model



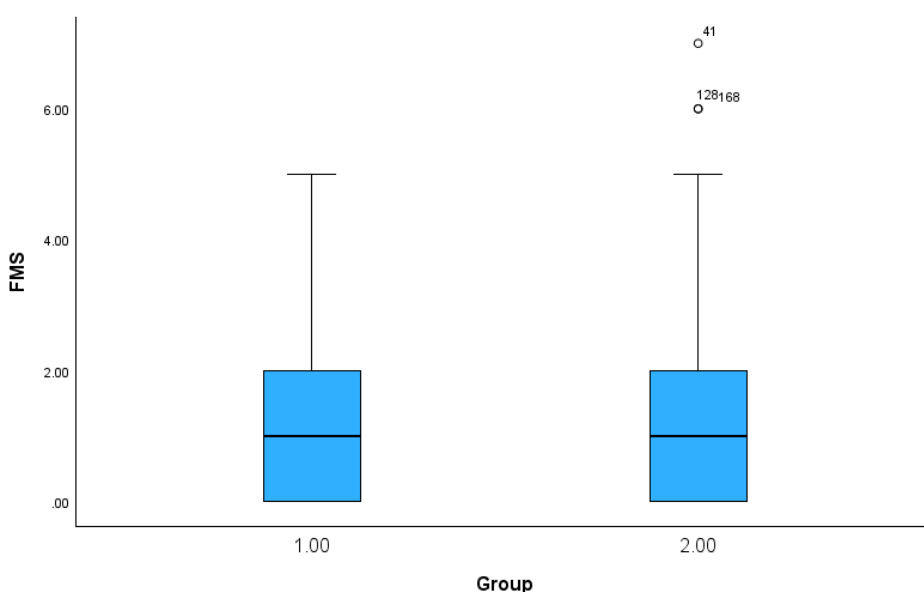
Note: NPE = non-preservative errors

Figure 15 shows Boxplots for both the treatment (high BIS-11 Factor I motor impulsivity) and control (low FI-MI) groups for FMS for the WCST model. The boxes for the treatment (high FI-MI, Group 2 in Figure 15) and the control (low FI-MI, Group 1 in Figure 15)

group both show virtually identical central tendencies in the interquartile range (*IQR*; middle 50%). The median line in the Boxplot also suggests an equally distributed *IQR* for both groups with a zero effect. Whiskers ($1.5 \times IQR$) also show identical distributions for the treatment (high FI-MI) group and the control (low FI-MI) group. The control group had no outliers. The treatment group had two positive outliers and no extreme outliers. Overall, the Box plots suggest that FMS does not distinguish high BIS-11 Factor I trait motor impulsivity and low FI-MI on the WCST measure.

Figure 15

Boxplots of FMS for Treatment and Control Groups for the WCST Model



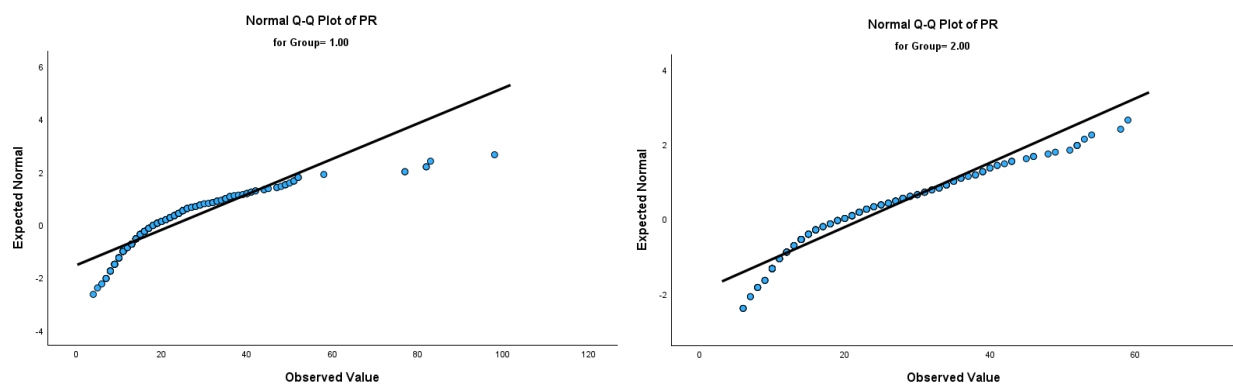
Note: FMS = failure to maintain set.

Figure 16 shows Q-Q Plots (Quantile-Quantile Plots) for PR for both Group 1 (the control, low BIS-11 FI motor impulsivity group) and Group 2 (the treatment, high FI-MI group) for the WCST model. The diagonal line represents a putative normal distribution. Both groups

confirm moderate non-normality consistent with the Box plots with the treatment group showing greater normality than the control group, which shows a bimodal tendency in that a subgroup of low FI motor impulsive individuals demonstrating some extreme perseverative responses (preservation).

Figure 16

Q-Q Plots of Treatment and Control Groups for PR for the WCST Model

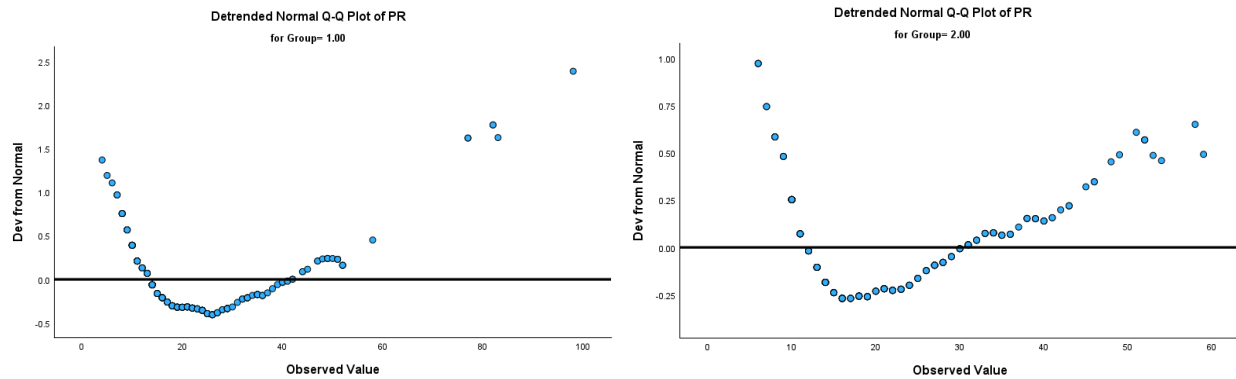


Note: PR = preservative response.

Figure 17 shows a detrended normal Q-Q plot of PR for the WCST model, which shows the residuals (quantile delimited on y-axis) between observed and expected normal PR values for each of the control (low FI-MI) and treatment (high FI-MI) groups. The control group shows significant platykurtic bimodal tendency with a subpopulation within this group, while the treatment group presents a unimodal distribution closer to normality, confirming previous findings.

Figure 17

Detrended Normal Q-Q Plot of PR for the WCST Model

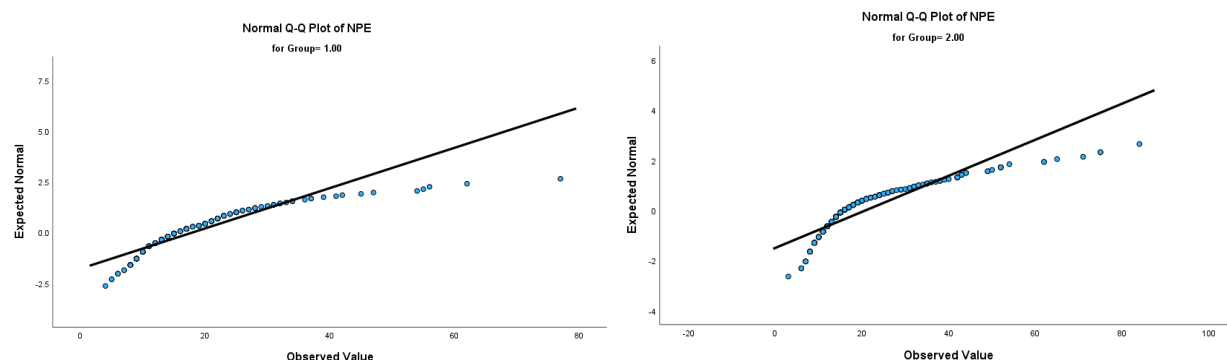


Note: PR = preservative errors.

Figure 18 shows Q-Q Plots (Quantile-Quantile Plots) for NPE in the WCST model for both Group 1 (the control, low BIS-11 FI motor impulsivity group) and Group 2 (the treatment, high FI-MI group). The diagonal line represents a putative normal distribution. Both groups also show a substantially normal distribution, contrasting with the results for PR above as to the control group. Results confirm earlier findings of a measurable and potentially significant difference (higher NPE) for the high FI-MI treatment group versus the control (low FI-MI) group.

Figure 18

Q-Q Plots of Treatment and Control Groups for NPE for the WCST Model

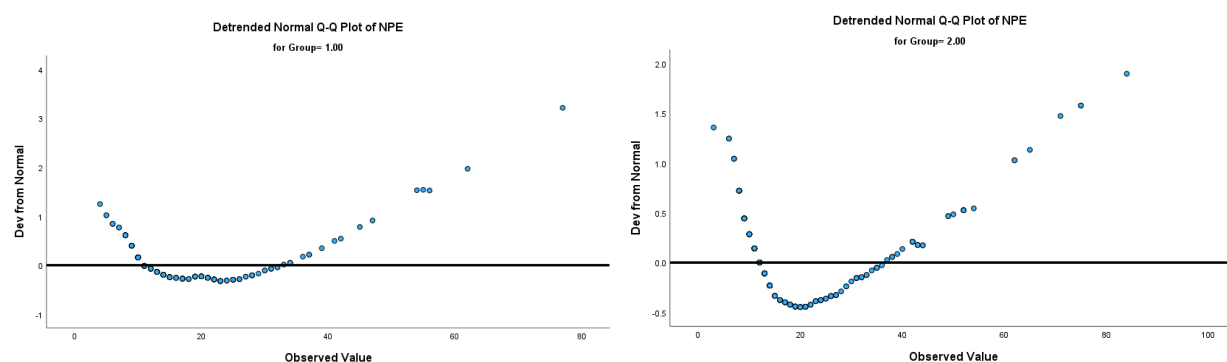


Note: NPE = non-perseverative errors

Figure 19 shows a detrended (extracting any reference to mean and variance) normal Q-Q plot of NPE for the WCST model which shows the residuals (quantile delimited on y-axis) between observed and expected normal NPE values for each of the control (low FI-MI) and treatment (high FI-MI) groups. Both plots suggest greater non-normality than suggested by the normal Q-Q plots above for NPE, with a systematic U-shaped pattern with greater deviation for the control group.

Figure 19

Detrended Normal Q-Q Plot of NPE for the WCST Model

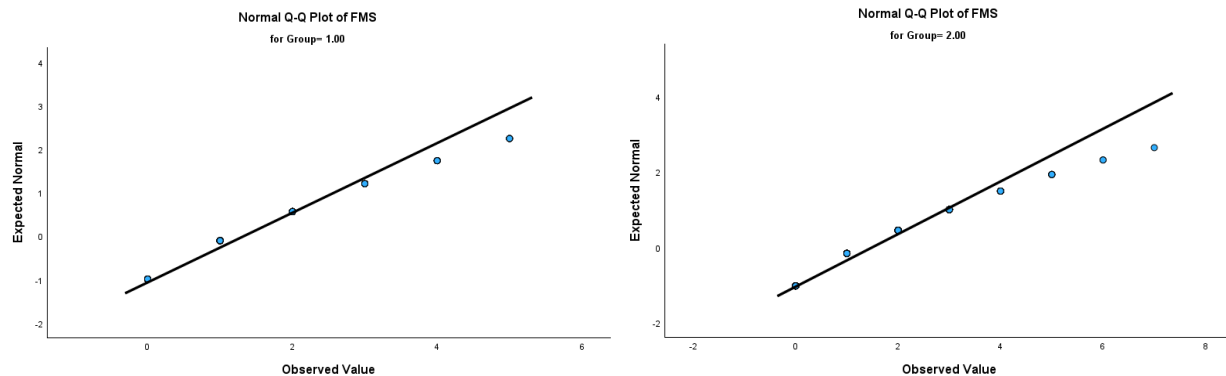


Note: NPE = non-perseverative errors.

Figure 20 shows Q-Q Plots (Quantile-Quantile Plots) for FMS for the WCST model for both Group 1 (the control, low BIS-11 FI motor impulsivity group) and Group 2 (the treatment, high FI-MI group). The severe floor effects of the FMS subscale of the WCST limits interpretability of the normal Q-Q plot. The control group indicates an extreme, highly platykurtic, positive skew (heavy right tail) with the treatment group demonstrating a distribution closer to normal. The tendency of low FI-MI individuals to commit FMS errors may limit utility of this subscale to identify significant group differences.

Figure 20

Q-Q Plots of Treatment and Control Groups for FMS for the WCST Model



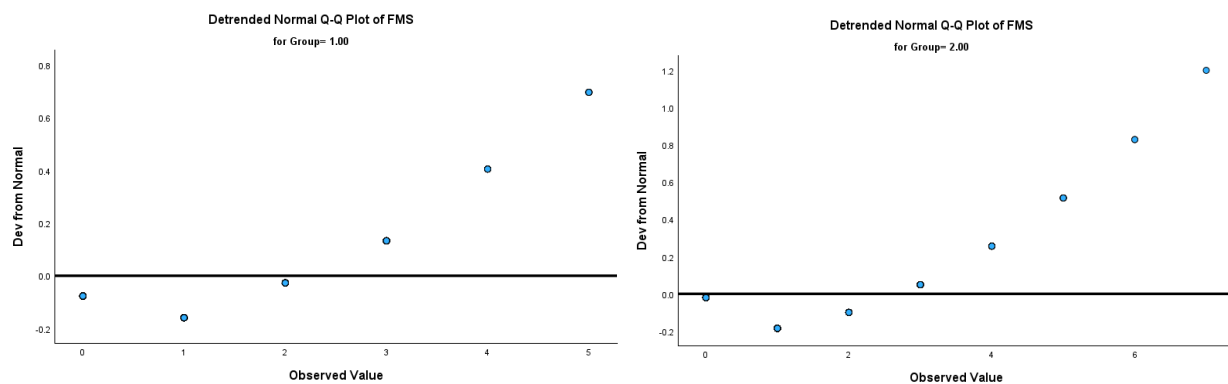
Note: FMS = failure to maintain set.

Figure 21 shows a detrended normal Q-Q plot of FMS for the WCST model which shows the residuals (quantile delimited on y-axis) between observed and expected normal FMS values for each of the control (low FI-MI) and treatment (high FI-MI) groups. The detrended Q-Q plots contradict results for the normal Q-Q plots in that the treatment Group 2 (high FI-MI) suggests

worse detrended normality than the control Group 1(low FI-MI). Again, the floor effects confirm possible issues with MANOVA analysis utility and normality assumptions.

Figure 21

Detrended Normal Q-Q Plot of FMS for the WCST Model



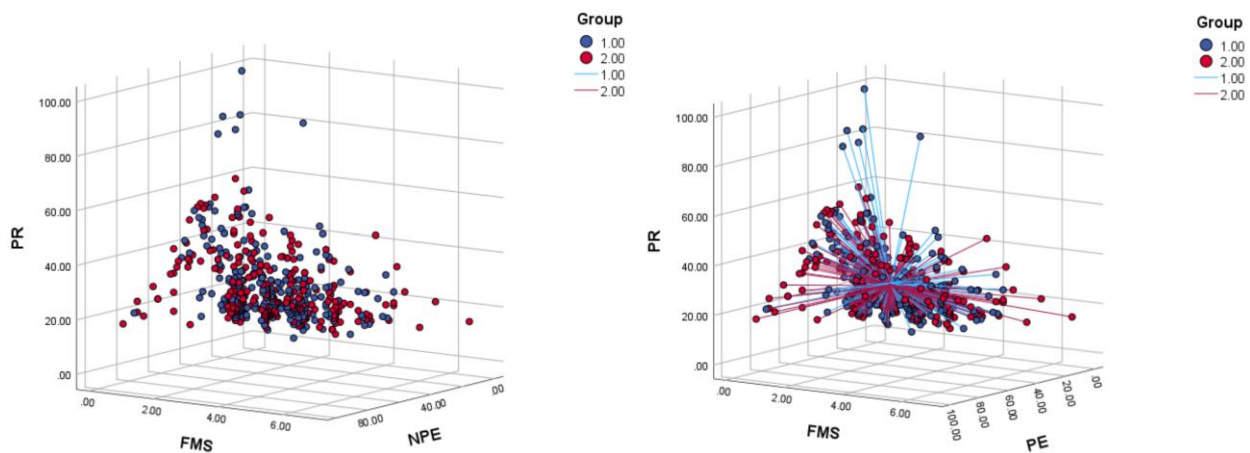
Note: FMS = failure to maintain set.

Figure 22 shows three-dimensional scatter plots, with and without centroids, of the three dependent (outcome) variables of PR, NPE, and FMS for the WCST model by independent (predictor) variable categorical group of low (Group 1) and high (Group 2) Factor I motor impulsivity (FI-MI) scores on the BIS-11. Figure 22 shows the interaction between the dependent (outcome) variables by group membership. Overlapping positively intercorrelated clusters suggest that the groups do not significantly differ on the dependent variables, requiring more quantitative analysis via MANOVA and post hoc testing to tease out any statistically significant differences. The differences are more dimensional than categorical. FMS floor effects limit differentiators of the linear combination of dependent variables. PR and NPE are positively correlated as indicated by other measures. Counterintuitively, as suggested previously, the

control group appears to have more cognitive variability (distinct from motor impulsivity) than the treatment group. Centroids suggest systematic differences between the high BIS-1 Factor I motor impulsivity (treatment) group and the low FI-MI (control) group.

Figure 22

Three-Dimensional Scatter Plot Matrix/Centroid by H-FIMI and L-FIMI for The WCST Model

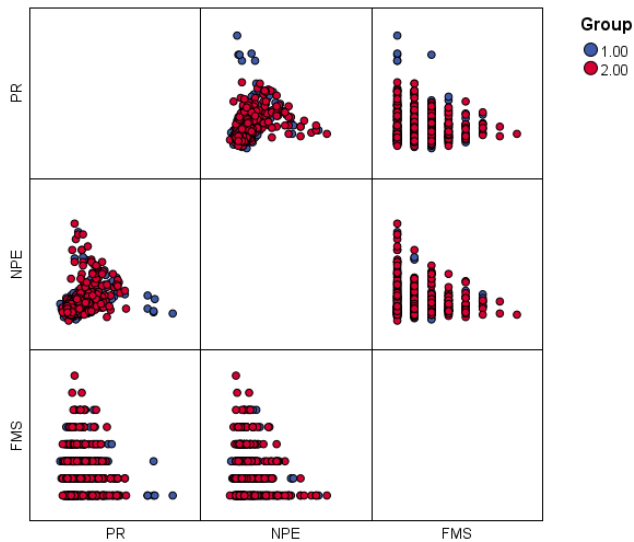


Note: PR = perservative responses.

Figure 23 shows a scatter plot matrix to illustrate the pairwise relationships between the three dependent (outcome) variables of PR, NPE, and FMS for the WCST model. PR and NPE are positively linearly correlated, consistent with observations from above. FMS floor effects are confirmed by the scatterplot matrix.

Figure 23

Scatterplot Matrix of PR, NPE, and FMS for the WCST Model



Note: PR = preservative responses, NPE = non-perseverative errors, FMS = failure to maintain set.

Results For Research Question 1 (RQ1), H1, WCST Model

A one-way (one-factor) between-subjects unpaired multivariate analysis of variance (MANOVA) was conducted to examine the effect of the dichotomous (categorical) independent predictor variable groupings (factor levels) of top and bottom quartile Factor I (FI) motor impulsivity (MI) scores on the BIS-11 on three dependent (outcome) variables of perseverative responses (PR), non-perseverative errors (NPE), and failure to maintain set (FMS) of the Wisconsin card sorting test (WCST). Analysis of the MANOVA results in SPSS-30 revealed a statistically significant effect of BIS-11 FI motor impulsivity (MI) dichotomous independent (predictor) variable group (low MI [control] vs. high MI [treatment]) on the linear combination (variate) of the dependent (outcome) variables of PR, NPE, and FMS, $F(3, 476) = 2.785, p =$

.041, partial $\eta^2 = .017$. Univariate tests revealed a significant effect for NPE, $F(1,478) = 6.579$, $p = .011$, partial $\eta^2 = .014$, with small effect indicating that the high BIS-11 FI-MI treatment group demonstrated significantly more non-perseverative errors (NPE) than the low BIS-11 FI-MI control group, reflecting poorer cognitive flexibility and set-shifting ability as measured by the WCST. No significant effects were found for PR, $F(1,478) = 0.114$, $p = .736$, partial $\eta^2 = .000$; or FMS, $F(1,478) = 2.037$, $p = .154$, partial $\eta^2 = .004$. Post hoc tests were conducted using independent samples t -tests to identify which dependent variable was responsible for the significant MANOVA result, confirming that NPE was the sole contributor to the multivariate effect. Details of the multivariate, univariate, and post-hoc tests are discussed below.

Multivariate Tests: MANOVA for the WCST Model

Table 23 shows the results of the multivariate tests for the WCST model (RQ1, Hypothesis 1) for the intercept of the WCST model and for the group variable. As mentioned previously, because the homogeneity of covariances assumption was violated, Pillai's Trace was more appropriate to determine the effect size of variance in the dependent outcome variables as explained by the independent predictor variable. Pillai's trace is also less sensitive to violations of the MANOVA assumptions. Pillai's trace, Pillai's $V = .024$, $F(3,476) = 3.889$, $p = .009$, indicated that the differences between the control (low BIS-11 FI motor impulsivity) and treatment (high FI-MI) groups were statistically significant. The effect size was small, partial $\eta^2 = .024$, indicating that 2.4% of the variance in the linear combination (linear variate) of PR, NPE, and FMS was explained by group membership. Comparison with other measures confirmed a significant effect. As discussed in Chapter 3, since there is only one linear variate (and one eigenvector and eigenvalue) due to the model (research question) containing only one independent predictor variable (factor) and two levels (groups) for each independent variable, it

was expected that the differences between the different calculations of the approximate F statistic would be similar. F values, statistic; $F(3,476) = 3.889$, support statistically significant group differences via the ratio of systematic variance to error variance. Consequently, Wilk's Lambda (the proportion of variance of the dependent outcome variables that is not explained by the independent predictor variable) also showed significance and a small effect, Wilk's $\Lambda = 0.976$, $F(3,476) = 3.889$, $p = 0.009$, partial $\eta^2 = .024$; Hotelling's Trace also showed significance and a small effect, Hotelling's $T^2 = .025$, $F(3,476) = 3.889$, $p = .009$, partial $\eta^2 = .024$, as did Roy's Largest Root, Roy's $\theta = .025$, $F(3,476) = 3.889$, $p = .009$, partial $\eta^2 = .024$.

Table 23

Multivariate Tests for the WCST Model^a

Hypo					Partial	Noncent.	Obsvd.	
Effect	Value	F	df	Error df	p	η^2	Param.	Power ^c
Intercept								
Pillai's V	.862	993.040 ^b	3.000	476.000	<.001	.862	2979.119	1.000
Wilks' Λ	.138	993.040 ^b	3.000	476.000	<.001	.862	2979.119	1.000
Hotelling's T^2	6.259	993.040 ^b	3.000	476.000	<.001	.862	2979.119	1.000
Roy's θ	6.259	993.040 ^b	3.000	476.000	<.001	.862	2979.119	1.000
Group								
Pillai's V	.024	3.889 ^b	3.000	476.000	.009	.024	11.667	.825
Wilks' Λ	.976	3.889 ^b	3.000	476.000	.009	.024	11.667	.825
Hotelling's T^2	.025	3.889 ^b	3.000	476.000	.009	.024	11.667	.825
Roy's θ	.025	3.889 ^b	3.000	476.000	.009	.024	11.667	.825

^a Design: Intercept + Group. ^b Exact statistic, ^c Computed using $\alpha = .05$

The observed power for the WCST model of .825 indicates that there was an 82.5% chance of finding the observed effect to be statistically significant in the sample of 480 participants. This exceeds the optimal power commonly accepted in the literature that would indicate that there is at least an 80% chance of finding an observed effect (Cohen, 1988). Consequently, the null hypothesis (H_{I_o}) for Research Question 1, Hypothesis 1 can be rejected and the alternate hypothesis can be accepted (H_{I_a}). This is confirmed by the group differences discussed previously, particularly with respect to NPE and unique effects for PR as to the control group.

Table 24 shows the results of Levene's Test for Equality of Variances for each of the dependent (outcome) variables of PR, NPE, and FMS. Using mean as the basis, the p values show mixed results for the assumption of homogeneity of variance (homoscedasticity). While the assumption is met for PR, $F(1, 478) = 2.110, p = .147$, it is violated for NPE, $F(1, 478) = 16.515, p < .001$, and for FMS, $F(1, 478) = 3.911, p = .049$. NPE showed a clear significant violation of the equal variances assumption, while FMS was marginally significant. Note that median and trimmed mean results provide robust support for the above findings, with NPE consistently showing significance across all methods, $p = .007$ for median, $p < .001$ for trimmed mean, and FMS showing marginal significance, $p = .125$ for median, $p = .052$ for trimmed mean.

Table 24*Levene's Test of Equality of Error Variances^a for the WCST Model*

	Levene's <i>F</i>	<i>df1</i>	<i>df2</i>	<i>p</i>
PR				
Based on Mean	2.110	1	478	.147
Based on Median	.723	1	478	.395
Based on Median and with adjusted <i>df</i>	.723	1	397.477	.396
Based on trimmed mean	1.265	1	478	.261
NPE				
Based on Mean	16.515	1	478	<.001
Based on Median	7.285	1	478	.007
Based on Median and with adjusted <i>df</i>	7.285	1	426.630	.007
Based on trimmed mean	12.421	1	478	<.001
FMS				
Based on Mean	3.911	1	478	.049
Based on Median	2.365	1	478	.125
Based on Median and with adjusted <i>df</i>	2.365	1	459.876	.125
Based on trimmed mean	3.787	1	478	.052

Note: Tests the null hypothesis that the error variance of the dependent variable is equal across groups. PR = preservative responses, NPE = non-perseverative errors, FMS = failure to maintain set.

^a Design: Intercept + Group

Table 25 shows the results of tests of between-subject effects via the univariate F s (separate univariate ANOVAs) for each dependent (outcome) variable of PR, NPE, and FMS for the WCST. This test informs determination of statistically significant differences between the two predictor groups (treatment, high FI-MI, or control, low FI-MI) on each individual dependent (outcome) variable. The results for the model sum of squares for the groups shows no statistically significant differences between groups for PR, $F(1,478) = 0.114, p = .736$, partial $\eta^2 = .000$, and FMS, $F(1,478) = 2.036, p = .154$, partial $\eta^2 = .004$, and a statistically significant difference between groups for NPE with small effect, $F(1,478) = 6.580, p = .011$, partial $\eta^2 = .014$. This suggests that, to the extent that there were group differences, NPE was the primary contributor to those differences. As noted previously, the treatment group (high FI-MI, Group 2) had a higher mean NPE score, $\bar{x} = 20.88, SD = 13.9$, than the control group (low FI-MI, Group 1, $\bar{x} = 18.0, SD = 10.1$). As described in Chapter 2, NPE is also an indicator of cognitive flexibility and set-shifting ability (NPEs occur upon failure to maintain or appropriately shift mental states). Consequently, the high BIS-11 FI-MI treatment group demonstrates practically poorer executive control than the low BIS-11 FI-MI control group. The corrected model shows the total sums of squares, which demonstrates how much variance is explained by all predictors (independent variable factor levels) in the WCST model. Values for the corrected models were identical to the

group model because there were no covariates in the model so the corrected model is simply the effect of group plus the intercept.

Table 25

Tests of Between-Subjects Effects for the WCST Model

	Type III Sum						partial	Noncent.	Observed
Sourc DV	of Squares	<i>df</i>	Mean Square	<i>F</i>	<i>p</i>	η^2	Parameter	Power ^d	
Corrected Model									
PR	20.419 ^a	1	20.419	0.114	.736	.000	0.114		.063
NPE	971.852 ^b	1	971.852	6.580	.011	.014	6.580		.726
FMS	3.675 ^c	1	3.675	2.036	.154	.004	2.036		.296
Intercept									
PR	249021.852	1	249021.852	1390.359	<.001	.744	1390.359		1.000
NPE	181701.919	1	181701.919	1230.303	<.001	.720	1230.303		1.000
FMS	963.333	1	963.333	533.578	<.001	.527	533.578		1.000
Group									
PR	20.419	1	20.419	0.114	.736	.000	.114		.063
NPE	971.852	1	971.852	6.580	.011	.014	6.580		.726
FMS	3.675	1	3.675	2.036	.154	.004	2.036		.296
Error									
PR	85612.729	478	179.106						
NPE	70595.229	478	147.689						
FMS	862.992	478	1.805						

		Type III Sum					partial	Noncent.	Observed
Sourc	DV	of Squares	<i>df</i>	Mean Square	<i>F</i>	<i>p</i>	η^2	Parameter	Power ^d
Total									
	PR	334655.000	480						
	NPE	253269.000	480						
	FMS	1830.000	480						
Corrected Total									
	PR	85633.148	479						
	NPE	71567.081	479						
	FMS	866.667	479						

Note: PR = preservative responses, NPE = non-perseverative errors, FMS = failure to maintain set.

^a $R^2 = .000$ (Adjusted $R^2 = -.002$). ^b $R^2 = .014$ (Adjusted $R^2 = .012$). ^c $R^2 = .004$ (Adjusted $R^2 = .002$). ^d Computed using $\alpha = .05$

Table 26 shows parameter estimates for WCST model (RQ1, Hypothesis 1) for each dependent (outcome) variable of PR, NPE, and FMS. In this study, parameter estimates were not necessary because there were no covariates, although parameter estimates can be useful for determining the magnitude and direction of effects of the independent (predictor) variable on the dependent variables, as well as test, confirm, or support interpretation of main effects, Levene's test, and tests of between-subject effects via univariate *F*s (Field, 2024; George & Mallery, 2024). There was a statistically significant result for NPE, $B = -2.846$, $p = .011$, and partial $\eta^2 = 0.014$, with no statistically significant result for PR, $B = .413$, $p = .736$, partial $\eta^2 = 0.000$, or

FMS, $B = -.175$, $p = .154$, partial $\eta^2 = .004$, which was consistent with the other tests. Note that the B statistic is negative because SPSS-30 sets the first numerical category (the low FI-MI control group in this case) as the reference group and, as such, the statistics are relative to the other group (the high FI-MI treatment group), which is set at zero. Overall, the observed power of NPE of .726 indicated good power to detect a small, but potentially meaningful effect consistent with the literature that motor impulsivity is associated with cognitive flexibility and set-shifting deficits as measured by non-perseverative errors (NPE) in the WCST.

Table 26

Parameter Estimates for the WCST Model

95% Confidence										
DV	Parameter	<i>B</i>	Std. Err	<i>t</i>	<i>n</i>	Interval		Partial	Noncent.	Observed
						Lower	Upper	η ²	Parameter	Power ^b
PR										
	Intercept	22.571	0.864	26.128	<.001	20.873	24.268	.588	26.128	1.000
	[Group=1.00]	.413	1.222	0.338	.736	-1.988	2.813	.000	0.338	.063
	[Group=2.00]	0 ^a	.	.	.	.	.	.	.	.
NPE										
	Intercept	20.879	0.784	26.616	<.001	19.338	22.421	.597	26.616	1.000
	[Group=1.00]	-2.846	1.109	-2.565	.011	-5.026	-0.666	.014	2.565	.726
	[Group=2.00]	0 ^a	.	.	.	.	.	.	.	.
FMS										
	Intercept	1.504	0.087	17.343	<.001	1.334	1.675	.386	17.343	1.000

95% Confidence										
DV	Parameter	<i>B</i>	Std. Err	<i>t</i>	<i>n</i>	Interval		Partial η^2	Noncent. Parameter	Observed Power ^b
						Lower	Upper			
	[Group=1.00]	-.175	0.123	-1.427	.154	-0.416	0.066	.004	1.427	.296
	[Group=2.00]	0 ^a	.	.	.	.	.	.	.	.

Note: PR = preservative responses, NPE = non-perseverative errors, FMS = failure to maintain set.

^a This parameter is set to zero because it is redundant. ^b Computed using $\alpha = .05$.

Between-Subjects SSCP Matrix for the WCST Model

Table 27 shows the between-subjects sum of squares cross product (SSCP) matrices of the WCST model. The SSCP matrices are foundational precursors to calculation of eigenvalues for the *F* statistic and used to explore the pattern of the data via cross-products (uncentered covariance matrix or features to build covariance matrices) to characterize the relationship (covariability) between the dependent (outcome) variables of PR, NPE, and FMS. As noted in Chapter 3's discussion of MANOVA mathematics, the SSCP is calculated in MANOVA, after extracting the eigenvalue from the eigenvector (more precisely, after extracting eigenvalues from the SSCP matrices and then eigenvectors from those eigenvalues) for each dependent (outcome) variable, via least squares regression to calculate the sum of squares. Then, MANOVA calculates the sum of squares of the error (within groups unsystematic residual variance) and then total sum of squares. Next (simultaneously as part of matrix operations), MANOVA calculates the sum of the cross-product covariance (via matrix and linear algebra) and finally the SSCP matrices. SSCP

matrices thus enable MANOVA to consider cross correlations between the dependent (outcome) variables, which ANOVAs cannot do.

The hypothesis intercept matrix in Table 27 provides the total variability of the model resulting primarily from the intercept. The group matrix in Table 27 provides the sum of squares and cross product (SSCP) output to characterize the effect of the independent (predictor) variable of FI-MI (high and low groups) on group differences of the dependent (outcome) variables. The error matrix below that on the table provides the residual variance in light of group differences. The group diagonals represent the sum of squares (*SS*) and the off-diagonals represent the cross-products (*CP*). Thus, the diagonals, $PR = 20.419$, $NPE = 971.852$, $FMS = 3.675$, show the magnitude of how much variance each dependent (outcome) variable contributes to the group difference. The hypothesis sum of squares for NPE (971.852) is much larger than that for PR and FMS, supporting the previous observations regarding the effect of the NPE dependent (outcome) variable. Negative off-diagonals indicate negative relationships (correlations) between PR and NPE (-140.869) and between PR and FMS (-8.663), while the positive off-diagonal between NPE and FMS (59.762) indicates a positive relationship.

The within group error matrix represents unexplained variability in the model. The diagonal for PR, NPE, and FMS contain values indicating high variance (determinants) in PR (85612.729) and PE (70595.229), but lower values for FMS (862.992). Off-diagonal negative cross product values in the error matrix suggest negative correlations between PR and FMS (-1192.754) and between NPE and FMS (-1457.013), while the positive cross product between PR and NPE (27292.688) suggests a positive correlation. Because the error variance is significantly higher than the group variance (4,191 times larger for PR, 73 times larger for NPE, 235 times larger for FMS), the SSCP matrices support the previous indicators that, notwithstanding NPE

having statistical significance, BIS-11 FI-MI predicts a very small fraction of the total variance in performance in the WCST laboratory behavioral measure. This is also consistent with the relationship between the WCST and cognitive flexibility.

Table 27

Between-Subjects SSCP Matrix for the WCST Model

		PR	NPE	FMS
Hypothesis	Intercept			
	PR	249021.852	212715.181	15488.417
	NPE	212715.181	181701.919	13230.250
	FMS	15488.417	13230.250	963.333
	Group			
	PR	20.419	-140.869	-8.663
	NPE	-140.869	971.852	59.762
	FMS	-8.663	59.762	3.675
Error				
	PR	85612.729	27292.688	-1192.754
	NPE	27292.688	70595.229	-1457.013
	FMS	-1192.754	-1457.013	862.992

Note: Based on Type III Sum of Squares. PR = preservative responses, NPE = non-perseverative errors, FMS = failure to maintain set.

Table 28 shows the residual SSCP matrices for the WCST model. It contains the variance-covariance (mean sum of squares-mean cross product) matrix (variance-covariance matrix derived from the SSCP matrix) and the correlation matrix. As described in Chapter 3, this measure interrogates any error (unexplained variance [discriminant]) and covariances after fitting the model (WCST model in this case).

Starting with the correlation matrix, the diagonals of unity represent perfect self-variable correlation and off-diagonals characterize the direction and strength of relationships among the three dependent (outcome) variables of PR, NPE, and FMS. Standardizing the covariance matrix here yields Pearson correlation coefficients (r). The results indicate a moderate positive correlation, $r = .351$, between PR and NPE, weak negative correlations between PR and FMS, $r = -.139$, and between NPE and FMS, $r = -.187$. These results suggest that PR and NPE share some common variance, while FMS demonstrates different patterns from both PR and NPE. The diagonal of the residual SSCP matrix array contains high values, PR = 85612.729, PE = 70595.229, FMS = 862.992, suggesting significant residual variability, particularly for PR and NPE. The shared covariance suggests minimal multicollinearity concerns for MANOVA assumptions, with correlations well within acceptable ranges and no indication of variable redundancy. The negative off-diagonal values for the cross-products of PR and FMS (-1192.754) and NPE and FMS (-1457.013) suggest that these variables covary inversely. Overall, the correlational structure confirms the dominance of NPE for multivariate effects in the WCST model.

Table 28*Residual SSCP Matrix for the WCST Model*

	PR	NPE	FMS
Sum-of-Squares and Cross-Products			
PR	85612.729	27292.688	-1192.754
NPE	27292.688	70595.229	-1457.013
FMS	-1192.754	-1457.013	862.992
Covariance			
PR	179.106	57.098	-2.495
NPE	57.098	147.689	-3.048
FMS	-2.495	-3.048	1.805
Correlation			
PR	1.000	.351	-.139
NPE	.351	1.000	-.187
FMS	-.139	-.187	1.000

Note: Based on Type III Sum of Squares. PR = preservative responses, NPE = non-perseverative errors, FMS = failure to maintain set.

Table 29 shows the estimated marginal means describing the adjusted means for each dependent (outcome) variable of PR, NPE, and FMS by dichotomous group (BIS-11 low FI-MI [Group 1], and high FI-MI [Group 2]). The treatment group (high FI-MI) had higher NPE, $\bar{x} = 20.879$, [19.338, 22.421], $SE = .784$, than the control group (low FI-MI), $\bar{x} = 18.033$, [16.492, 19.575], $SE = .784$. The confidence intervals effectively do not overlap and do not pass zero,

representing practical significance ($p = .011$). The difference between the treatment group (high FI-MI), $\bar{x} = 22.571$ [20.873, 24.268], $SE = .864$, and the control group (low FI-MI), $\bar{x} = 22.983$ [21.286, 24.681], $SE = .864$, for PR was insignificant, with heavily overlapping confidence intervals. Similarly, the difference between the treatment group (high FI-MI), $\bar{x} = 1.504$ [1.334, 1.675], $SE = .087$, and the control group (low FI-MI), $\bar{x} = 1.329$ [1.159, 1.500], $SE = .087$, for FMS was insignificant with overlapping confidence intervals. Overall, the triangulation between descriptive statistics, parameter estimates, and marginal means confirm the previous results of NPE driving the significant multivariate differences between BIS-11 high FI-MI and low FI-MI treatment and control groups found in the MANOVA model. The significant effect of NPE, $p = .011$, serves as the primary predictor of differences in cognitive flexibility and set-shifting ability between high trait BIS-11 Factor I motor impulsivity (FI-MI) and low FI-MI, contributing to the significant multivariate effect observed across the linear combination of the three dependent variables of PR, NPE, and FMS for the WCST.

Table 29

Estimated Marginal Means for the WCST Model

DV	Group	$\bar{x}$	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
PR	Control (L-FIMI)	22.983	.864	21.286	24.681
	Treatment (H-FIMI)	22.571	.864	20.873	24.268
NPE	Control (L-FIMI)	18.033	.784	16.492	19.575
	Treatment (H-FIMI)	20.879	.784	19.338	22.421
FMS	Control (L-FIMI)	1.329	.087	1.159	1.500

DV	Group	$\bar{x}$	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
	Treatment (H=FIMI)	1.504	.087	1.334	1.675

Note: PR= perseverative responses; PE = preservative errors; FMS = failure to maintain set.

Group 1 = Low Factor I motor impulsivity (FI-MI; Control); Group 2 = High FI-MI (Treatment).

Post Hoc Tests for WCST Model

Since the MANOVA results indicate statistical significance between groups on a linear variate (combination) of the three dependent (outcome) variables of PR, NPE, and FMS, post hoc tests were run to identify (confirm from univariate tests) the source of the difference. Table 30 shows post hoc tests of pairwise comparisons for the Wisconsin card sorting test (WCST) model. As applied to this study, the tests of pairwise comparisons (with Bonferroni correction) comprise the practical equivalent of post MANOVA independent samples *t*-tests in cases where there is only one independent variable with two groups and pairwise comparisons test the difference between the two groups (high FI-MI vs. low FI-MI) for each dependent variable individually (PR, then NPE, then FMS). This is fundamentally similar to what independent samples *t*-tests do (independent samples *t*-tests were also run as described in Chapter 3 and are provided below pairwise comparisons). Consequently, pairwise comparisons examine the differences between the independent (predictive) variable dichotomous treatment (high BIS-11 FI motor impulsivity [MI]) and control (low FI-MI) groups on the three dependent (outcome) variables of perseverative responses (PR), non-perseverative errors (NPE), and failure to maintain set (FMS) for the WCST model.

The results of the pairwise comparisons in Table 30 show that, of the three dependent (outcome) variables, NPE was responsible for the statistical significance of the differences between the high FI-MI (treatment) and low FI-MI (control) groups. The treatment (high FI-MI) group (shown as Group 2 in Table 30) had a highly significant average of 2.846 greater number of non-perseverative errors (NPE) than the control group, Group 1; $SE = 1.109$, 95% CI [.666, 5.026], $p = .011$. Perseverative responses (PR) did not significantly contribute to group differences. The treatment (Group 2) group had a PR, on average, that was an insignificant 0.413 lower than control (Group 1) group, $SE = 1.222$, CI [-2.813, 1.988], $p = .736$. Failure to maintain set (FMS) also did not significantly contribute to group differences. The treatment (Group 2) group had, on average, a non-significant 0.175 greater failure to maintain set occurrences than the control (Group 1) group, $SE = .123$, CI [-.066, .416], $p = .154$.

Table 30

Pairwise Comparisons for the WCST Model

DV	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	p^a	95% Confidence Interval for Difference ^b	
						Lower Bound	Upper Bound
PR	1	2	0.413	1.222	.736	-1.988	2.813
	2	1	-0.413	1.222	.736	-2.813	1.988
NPE	1	2	-2.846*	1.109	.011	-5.026	-0.666
	2	1	2.846*	1.109	.011	0.666	5.026
FMS	1	2	-0.175	.123	.154	-0.416	0.066
	2	1	0.175	.123	.154	-0.066	0.416

Note: Based on estimated marginal means. Mean differences represent Group 1 (Control) minus Group 2 (Treatment). Negative values indicate higher scores in the Treatment group. CI = Confidence Interval; PR = perseverative responses; NPE = non-preserved errors. FMS = failure to maintain set.

^a $p < .05$ (significant), $p < .01$ (highly significant).

^b Adjustment for multiple comparisons: Bonferroni.

*. The mean difference is significant at the .05 level.

Table 31 shows the independent samples t -test for the WCST model (RQ1, Hypothesis 1) to identify which dependent variable is, or which variables are, responsible for the significance of the MANOVA results by comparing the means of the two groups for each dependent (outcome) variable. The results include statistics for equal variances assumed (EVA) and equal variances not assumed (EVNA), the latter in case the equality of variances assumption (homoscedasticity assumption) is violated. As previously reported, Levene's Test for Equality of Variances (homoscedasticity assumption) was violated for NPE (heteroscedasticity detected for NPE), and less so for FMS, but not for PR. Consequently, EVNA, which represents Welch's t -test, was reported for NPE and FMS, and EVA results, which represents the independent samples t -test, was reported for PR. Welch's t -test ignores the results (F statistic) from Levene's Test for Equality of Variances and adjusts the degrees of freedom by applying the Welch-Satterthwait equation below, which pools the degrees of freedom by taking an approximation of the effective degrees of freedom (df) of a linear variate (combination) of independent sample variances (Delacre et al., 2017; Ruxton, 2006).

(34)

$$v_{\chi'} \approx \frac{(\sum_{i=1}^n k_i s_i^2)^2}{\sum_{i=1}^n \frac{(k_i s_i^2)^2}{v_i}}$$

Where $v_{\chi'}$ are the approximate (non-analytical) degrees of freedom, k reflects the number of components, and s_i the standard deviation of the i^{th} component. Since the degrees of freedom differ between the independent samples (Student's) t -test (and the sample sizes are the same between groups) and Welch's t -test, the t -value will be identical, but the p -value will differ between the two (Delacre et al., 2017).

The results indicate that only one dependent (outcome) variable, NPE, is responsible for the significance of the MANOVA results, $p = .011$ [2-tailed]. Using EVNA, the t statistic for Welch's t -test (the mean difference for the two categorical predictor variables on NPE, divided by the standard error of the difference [essentially a signal to noise ratio]) was relatively large and the confidence interval did not cross zero, which supports statistical significance for NPE, $t(435.548) = -2.565$, $df = 435.548$, $MD = -2.846$, $\text{Std.E.} = 1.110$, 95% CI[-5.026, -.665]. For FMS, using EVNA, the results were not statistically significant, $t(469.373) = -1.427$, $df = 469.373$, $MD = -.175$, $\text{Std.E.} = .123$, 95% CI[-.416, .066], $p = .154$ [2-tailed]. Using EVA, PR, $F(1,478) = 2.110$, $t(478) = .338$, $p = .736$ [2-tailed], $MD = .413$, $\text{Std.E.} = 1.22$, 95% CI[-1.989, 2.813], had means that were not significantly different between groups.

Table 31*Independent Samples t-Tests for the WCST Model*

Levene's Test <i>t</i> -test for EOM										
					Significance		Mean	Std. Error	95% CIOD	
					1-Sid <i>p</i>	2-Sid <i>p</i>	Difference	Difference	Lower	Upper
<i>F</i>	<i>p</i>	<i>t</i>	<i>df</i>							
PR										
EVA	2.110	.147	.338	478	.368	.736	0.4123	1.223	-1.988	2.813
EVNA			.338	451.088	.368	.736	0.413	1.223	-1.988	2.813
NPE										
EVA	16.515	<.001	-2.565	478	.005	.011	-2.846	1.109	-5.026	-0.666
EVNA			-2.565	435.548	.005	.011	-2.846	1.109	-5.026	-0.665
FMS										
EVA	3.911	.049	-1.427	478	.077	.154	-0.175	0.122	-0.416	0.066
EVNA			-1.427	469.373	.077	.154	-0.175	0.122	-0.416	0.066

Note: PR = preservative responses, NPE = non-perservative errors, FMS = failure to maintain set. EVA = equal variances assumed, EVNA = equal variances not assumed. COID = confidence interval of the difference. EOM = equality of means.

Table 32 shows the effect sizes for the independent samples for WCST. The effect size for NPE demonstrated a small effect, Cohen's $d = -.234$, CI $[-.414, -.055]$, which is consistent with results of other tests previously described (supported by a confidence interval that did not include zero). The negative sign of the statistic indicates that the Factor I motor impulsivity BIS-11 values of the treatment (high) group had significantly more non-perseverative errors (NPE)

than the control (low) group. Neither PR, Cohen's $d = .031$, $CI[-.148, .210]$, nor FMS, Cohen's $d = -.130$, $CI[-.309, .049]$, demonstrated any statistically significant effects, also consistent with previous indicators. Consequently, the results of post hoc tests for sub-Research Questions RQ1a, RQ1b, and RQ1c support rejection of the sub-null hypothesis $H1b_0$ and acceptance of the sub-alternate hypothesis $H1b_A$, and acceptance of sub-null hypothesis $H1a_0$ and $H1c_0$, and rejection of sub-alternate hypothesis $H1a_A$ and $H1c_A$.

Table 32

Independent Samples Effect Sizes for the WCST Model

				95% Confidence Interval	
		Standardizer ^a	Point Estimate	Lower	Upper
PR	Cohen's d	13.383	.031	-.148	.210
	Hedges' g	13.404	.031	-.148	.209
	Glass's Δ	11.634	.035	-.144	.214
NPE	Cohen's d	12.153	-.234	-.414	-.055
	Hedges' g	12.172	-.234	-.413	-.054
	Glass's Δ	13.921	-.204	-.384	-.024
FMS	Cohen's d	1.344	-.130	-.309	.049
	Hedges' g	1.346	-.130	-.309	.049
	Glass's Δ	1.432	-.122	-.301	.057

Note: Cohen's d uses the pooled standard deviation. Hedges' correction uses the pooled standard deviation, plus a correction factor.

Glass's Δ uses the sample standard deviation of the control (i.e., the second) group. PR = preservative responses, NPE = non-perseverative errors, FMS = failure to maintain set.

^a The denominator used in estimating the effect sizes.

Research Question (RQ2), H2, The Go/No-Go (GNG) Model

RQ2 (Updated to Reflect Change in Sample Population)

Do linear variates of mean reaction time (mRt), commission errors (CE), and omission errors (OE) in the go/no-go (GNG) task differ between high and low motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults ages 18-40?

RQ2a. Is there a difference in mean reaction time (mRt) in the GNG task between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40?

RQ2b. Is there a difference in commission errors (CE) in the GNG task between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40?

RQ2c. Is there a difference in omission errors (OE) in the GNG task between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40?

H2₀ (Null Hypothesis)

Linear variates of mean reaction time (mRT), commission errors (CE), omission errors (OE) in the go/no-go (GNG) task do not differ between high and low motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults ages 18-40.

H2_a (Alternate Hypothesis)

Linear variates of mean reaction time (mRT), commission errors (CE), omission errors (OE) in the go/no-go (GNG) task differ between high and low motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults ages 18-40.

H2a₀. There is no difference in mean reaction time (mRt) in the GNG task between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H2aA. There is a difference in mean reaction time (mRt) in the GNG task between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H2b0. There is no difference in commission errors (CE) in the GNG task between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H2bA. There is a difference in commission errors (CE) in the GNG task between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

H2c0. There is no difference in omission errors (OE) in the GNG task between high and low motor impulsiveness subscale groups on the BIS-11 in adults 18-40.

H2cA. There is a difference in omission errors (OE) in the GNG task between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40.

Validity and Reliability of the Data: RQ2, Hypothesis 2: GNG Model

The GNG model demonstrated adequate psychometric properties in this study, supporting the construct validity concerns for the instrument addressed through use of optimized parameter settings described in Chapter 3. The implementation of Wessel's (2017) recommended parameters (pNoGo = .2, 1,500ms trial duration, 250 trials) appeared successful, as evidenced by the robust commission error (CE) effects ($p = .001$) and the theoretically consistent negative correlation between mean reaction time (mRt) and commission errors (CE; $r = -.259$). The strong discriminative power for BIS-11 Factor I trait motor impulsivity groups validated the parametric optimization approach and supports the instrument's utility for measuring prepotent response inhibition discussed in Chapter 3.

Table 33 shows the tests for normality. Taking into account the sample size (>50) the results of a Kolmogorov-Smirnov test were used to evaluate normality rather than the Shapiro-

Wilk test, which is better for small sample sizes. None of the three dependent (outcome) variables for Hypothesis 2 (GNG) were normally distributed, $p < .001$, by this measure.

Table 33

Tests for Normality for the GNG Model

		Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Group	Statistic	df	p	Statistic	df	p
mRt	Trmt	.188	240	<.001	.721	240	<.001
	Cont	.191	240	<.001	.760	240	<.001
CE	Trmt	.208	240	<.001	.703	240	<.001
	Cont	.204	240	<.001	.791	240	<.001
OE	Trmt	.339	240	<.001	.466	240	<.001
	Cont	.313	240	<.001	.533	240	<.001

Note: mRt = mean reaction time, CE = commission errors, OE = omission errors.

^a Lilliefors Significance Correction

Table 34 shows descriptive statistics for the GNG mean reaction time (mRt) dependent (outcome) variable for each of the high (treatment) and low (control) BIS-11 Factor I motor impulsivity (FI-MI) groups. If tests for normality do not pass, skewness and kurtosis at or close to zero may indicate oversensitivity of normality tests due to a large sample size. Skewness for mRt was high for both the low FI-MI - control (skewness = 3.039) and high FI-MI treatment (skewness = 2.162) groups, indicating a strongly positive distribution. Kurtosis was also high for control (kurtosis = 14.1) and treatment groups (kurtosis = 7.9) suggesting very heavy positive

tails in the data. Mean for mRt was slightly higher for the high FI-MI treatment group, $\bar{x} = 357.5$ ms, than the low FI-MI control group, $\bar{x} = 352.6$ ms.

Table 34

Descriptive Statistics for mRt for the GNG Model

		Control (Low FIMI)		Treatment (High FIMI)	
		Statistic	Std. Error	Statistic	Std. Error
mRt					
$\bar{x}$		352.6	6.004	357.5	6.471
95% Confidence Interval for	Lower Bound	340.8		344.7	
Mean	Upper Bound	364.4		370.2	
5% Trimmed Mean		342.1		346.3	
Median (<i>Mdn</i>)		335.3		340.0	
Variance (s^2)		8651.4		10050.2	
<i>SD</i>		93.0		100.3	
Minimum		131.8		3.7	
Maximum		935.9		839.6	
Range		804.1		835.9	
Interquartile Range (<i>IQR</i>)		63.23		76.1	
Skewness		3.039	.157	2.162	.157
Kurtosis		14.104	.313	7.865	.313

Note: mRt = mean reaction time, CE = commission errors, OE = omission errors.

Table 35 shows descriptive statistics for the GNG commission errors (CE) dependent (outcome) variable for each of the low (control) and high (treatment) BIS-11 Factor I motor impulsivity groups. Skewness for CE was high for both the control (skewness = 2.637) and treatment (skewness = 1.764) groups, indicating a strongly positive distribution. Kurtosis was also high for the control (kurtosis = 8.032) and treatment (kurtosis = 2.777) groups suggesting heavy positive tails in the data. Mean for the treatment (high FI-MI) group, $\bar{x} = 8.373$, was higher than for the control (low FI-MI) group, $\bar{x} = 5.944$, with non-overlapping 95% confidence intervals of 5.0 – 6.9 for the control group and 7.2 – 9.5 for the treatment group.

Table 35

Descriptive Statistics of CE for the GNG Model

	Control (Low FIMI)		Treatment (High FIMI)	
	Statistic	Std. Error	Statistic	Std. Error
CE				
$\bar{x}$	5.9441	.47130	8.3728	.579
95% Confidence Interval for Lower Bound	5.016		7.233	
Mean	Upper Bound	6.873	9.513	
5% Trimmed Mean	4.830		7.312	
Median (<i>Mdn</i>)	3.9900		4.990	
Variance (s^2)	53.310		80.392	
<i>SD</i>	7.301		8.966	
Minimum	0.00		0.00	
Maximum	41.00		40.00	

	Control (Low FIMI)		Treatment (High FIMI)	
	Statistic	Std. Error	Statistic	Std. Error
Range	41.00		40.00	
Interquartile Range (<i>IQR</i>)	6.00		8.90	
Skewness	2.637	.157	1.764	.157
Kurtosis	8.032	.313	2.777	.313

Note: mRt = mean reaction time, CE = commission errors, OE = omission errors.

Table 36 shows descriptive statistics for the GNG omission errors (OE) dependent (outcome) variable for each of the high (treatment) and low (control) BIS-11 Factor I motor impulsivity (FI-MI) groups. Skewness for OE was high for both the control (skewness = 3.495) and treatment (skewness = 3.551) groups, indicating a strongly positive distribution. Kurtosis was also high for control (kurtosis = 12.645) and treatment (kurtosis = 16.750), more so than CE, suggesting very heavy positive tails in the data.

Table 36

Descriptive Statistics of OE for the GNG Model

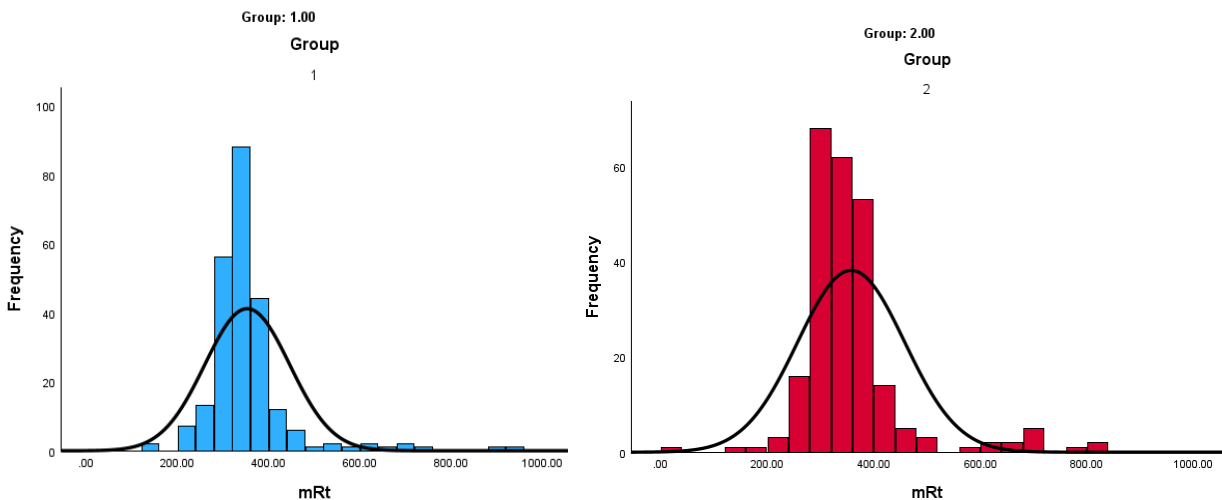
	Control (Low FI-MI)		Treatment (High FI-MI)	
	Statistic	Std. Error	Statistic	Std. Error
OE				
$\bar{x}$	8.647	1.347	11.904	1.580
95% Confidence Interval for Lower Bound	5.994		8.792	
Mean	Upper Bound	11.300	15.015	

	Control (Low FI-MI)		Treatment (High FI-MI)	
	Statistic	Std. Error	Statistic	Std. Error
5% Trimmed Mean	4.689		7.921	
Median (<i>Mdn</i>)	1.000		2.000	
Variance (s^2)	435.260		598.767	
<i>SD</i>	20.863		24.470	
Minimum	0.00		0.00	
Maximum	128.20		198.00	
Range	128.20		198.00	
Interquartile Range (<i>IQR</i>)	5.00		10.00	
Skewness	3.495	.157	3.551	.157
Kurtosis	12.645	.313	16.750	.313

As with the WCST model, histograms were run in SPSS to also test the normality assumption and boxplots and scatter plots for linearity and univariate outliers for the GNG model. Significant multivariate outliers were identified using Mahalanobis distance and Cook's distance. Histograms were run on all three dependent (outcome) variables. Generally, all frequency distributions of the dependent (outcome) variables did not meet normality assumptions. Figure 24 visually shows the results of histograms for the test of the linearity assumption for the treatment group (high FI-MI) and for the control group (low FI-MI) for mRt. The distributions were uniformly positively skewed as confirmed by the descriptive statistics shown at Table 34. All skew values were greater than 1.5, where 2 is a common threshold used in the context of the normality assumption.

Figure 24

Histograms of mRt Distribution for Treatment and Control Group for the GNG Model

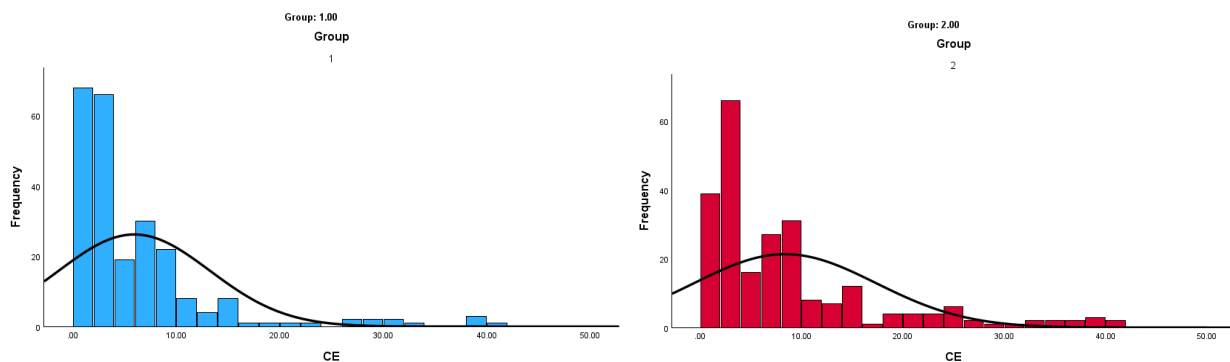


Note: mRt = mean reaction time. Group 1 = Factor I motor impulsivity (FI-MI) control group, Group 2 = Factor I motor impulsivity (FI-MI) treatment group.

Figure 25 visually shows the results of histogram for the test of the linearity assumption for the treatment group and the control group for CE. The distributions were heavily positively skewed as confirmed by the descriptive statistics shown at Table 35.

Figure 25

Histogram of CE Distribution for Treatment Group for the GNG Model

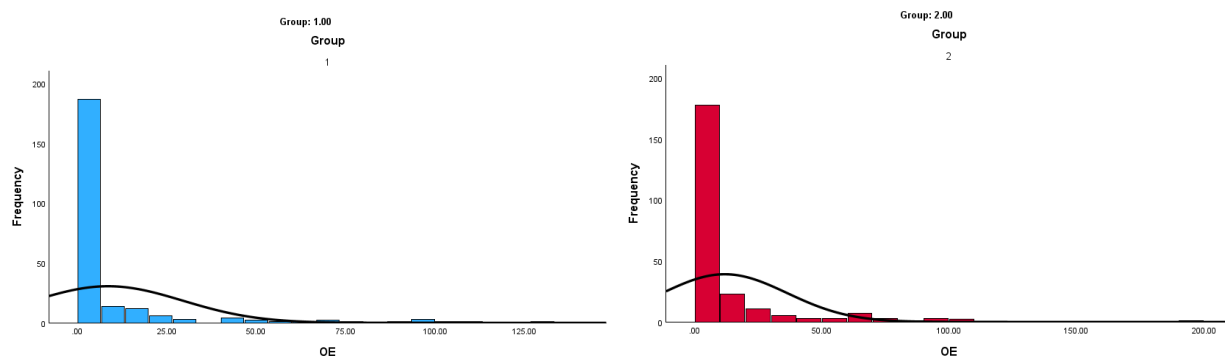


Note: CE = commission errors. Group 1 = Factor I motor impulsivity (FI-MI) control group, Group 2 = Factor I motor impulsivity (FI-MI) treatment group.

Figure 26 visually shows the results of histograms for the test of the linearity assumption for the treatment group and the control group for OE. The distributions were heavily positively skewed as confirmed by the descriptive statistics shown at Table 36.

Figure 26

Histogram of OE Distribution for Treatment Group for the GNG Model



Note: OE = omission errors. Group 1 = Factor I motor impulsivity (FI-MI) control group, Group 2 = Factor I motor impulsivity (FI-MI) treatment group.

With respect to multivariate outliers, Figure 27 shows Boxplots for both the treatment (high BIS-11 Factor I motor impulsivity) and control (low) groups for mRt for the GNG model. The boxes for both treatment (high FI-MI, Group 2 in Figure 27) and control (low FI-MI, Group1 in Figure 27) groups show relatively low variability in the interquartile range (*IQR*; middle 50%) of mRt values for both groups with the treatment group showing slightly more variability than the control group. The median lines in each plot show slightly positive skew for

the *IQR* of *mRt* values. Whiskers ($1.5 \times IQR$) also show greater variability for the treatment (high) group than the control (low) group. The control group had four positive outliers ($1.5 - 3 \times IQR$), nine extreme positive outliers ($>3 \times IQR$), and two negative outliers. The treatment group had one positive outlier, 11 extreme positive outliers, one negative outlier, and one extreme negative outlier. The outliers of the control (low) control group comprised 2.5% of cases (participants) and the extreme outliers comprised 3.8%. The outliers of the treatment (high) control group comprised 0.8% of cases and the extreme outliers comprised 5.0%.

Figure 27

Boxplots of mRt for Treatment and Control Groups for the GNG Model

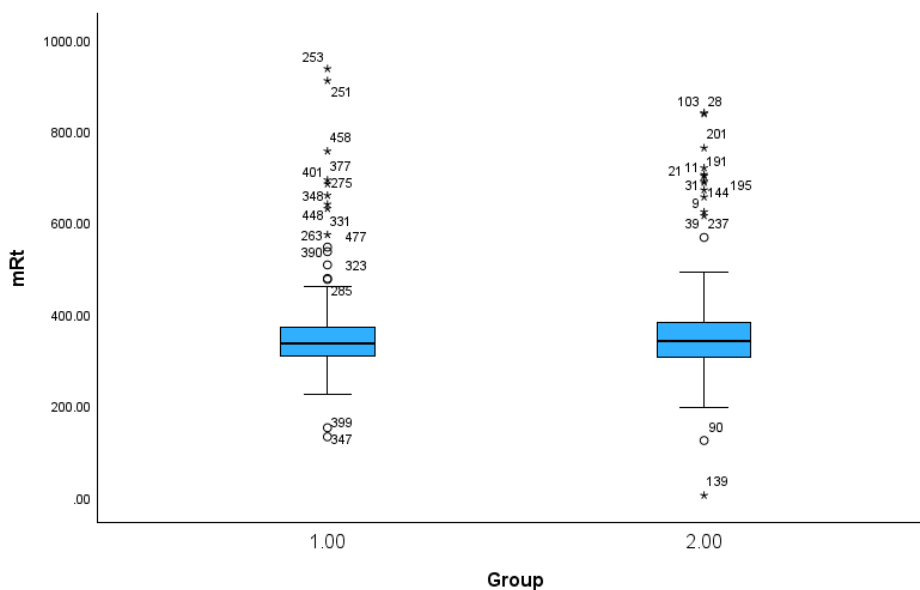


Figure 28 shows Boxplots for both the treatment (high BIS-11 Factor I motor impulsivity) and control (low FI-MI) groups for CE for the GNG model. The boxes for both treatment (high FI-MI, Group 2 in Figure 28) and control (low FI-MI, Group 1 in Figure 28) groups show relatively low variability in the interquartile range (*IQR*; middle 50%) of CE values for the control (low) group and significantly higher variability for the treatment (high) group.

The median line in the Boxplot suggests a normally distributed *IQR* for the control (low) group and a significantly positively skewed *IQR* for the treatment (high) group. Whiskers ($1.5 \times IQR$) also show greater variability for the treatment (high) group than the control (low) group. The control group had four positive outliers ($1.5 - 3 \times IQR$) and 11 extreme positive outliers ($>3 \times IQR$). The treatment group had nine positive outliers and three extreme positive outliers. The outliers of the control (low) control group comprised 1.7% of cases (participants) and the extreme outliers comprised 4.6%. The outliers of the treatment (high) control group comprised 3.8% of cases and the extreme outliers comprised 1.3%.

Figure 28

Boxplots of CE for Treatment and Control Groups for the GNG Model

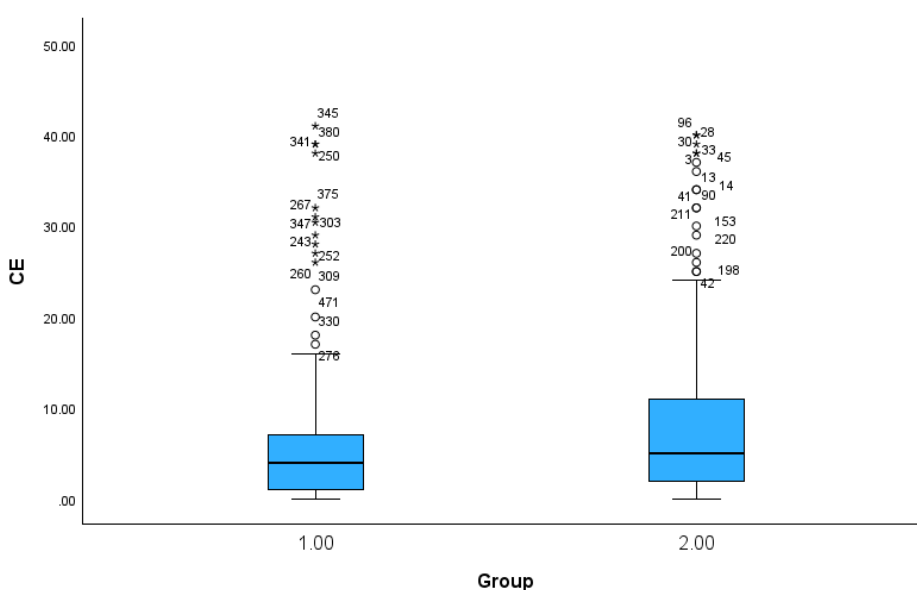


Figure 29 shows Boxplots for both the treatment (high BIS-11 Factor I motor impulsivity) and control (low FI-MI) groups for OE for the GNG model. The box for the treatment (high FI-MI, Group 2 in Figure 29) shows low variability in the interquartile range (IQR; middle 50%) and the box for the control (low FI-MI, Group 1 in Figure 29) group shows

extremely low variability. The median line in the Boxplot suggests a significantly positively skewed *IQR* for both groups. Whiskers ($1.5 \times IQR$) also show greater variability for the treatment (high FI-MI) group than the control (low FI-MI) group. The control group had four positive outliers ($1.5 - 3 \times IQR$) and 24 extreme positive outliers ($>3 \times IQR$). The treatment group had five positive outliers and 17 extreme positive outliers. The outliers of the control (low FI-MI) control group comprised 1.7% of cases (participants) and the extreme outliers comprised 10%. The outliers of the treatment (high FI-MI) control group comprised 2.1% of cases and the extreme outliers comprised 7.1%.

Figure 29

Boxplots of OE for Treatment and Control Groups for the GNG Model

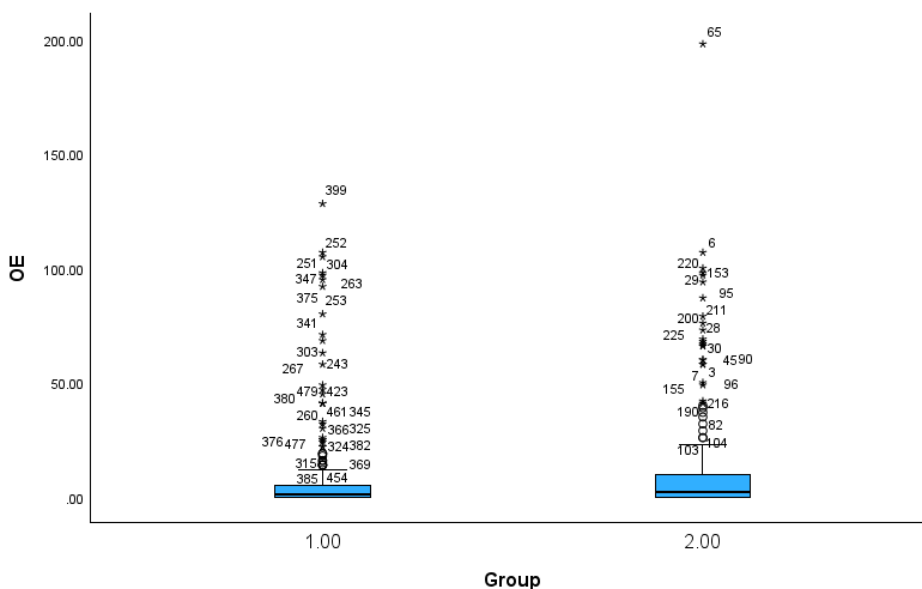
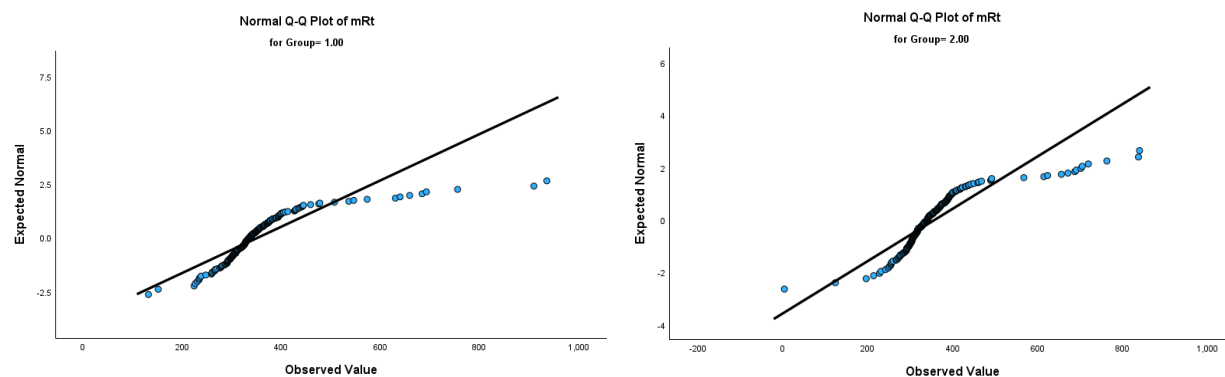


Figure 30 shows Q-Q Plots (Quantile-Quantile Plots) for mRt for both Group 1 (the control, low BIS-11 FI motor impulsivity group) and Group 2 (the treatment, high FI-MI group). The diagonal line represents a putative normal distribution. Both groups show a platykurtic distribution, demonstrating lightly tailed mRt data and relatively few outliers.

Figure 30

Q-Q Plots of Treatment and Control Groups for mRt for the GNG Model

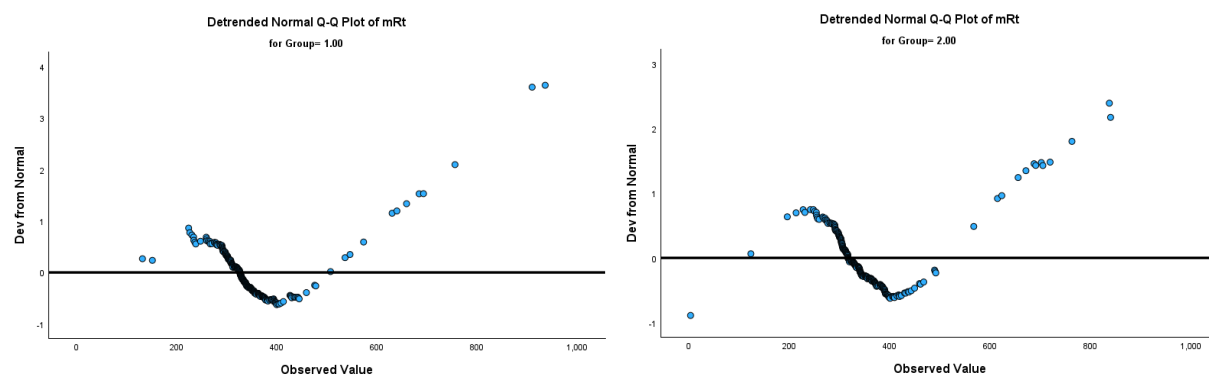


Note: mRt = mean reaction time.

Figure 31 shows a detrended normal Q-Q plot of mRt for the GNG task, which shows the residuals (quantile delimited on y-axis) between observed and expected normal mRt values (millisecond values on x-axis) for each of the control (low FI-MI) and treatment (high FI-MI) groups. Both plots demonstrate positively skewed tailed distributions.

Figure 31

Detrended Normal Q-Q Plot of mRt for the GNG Model

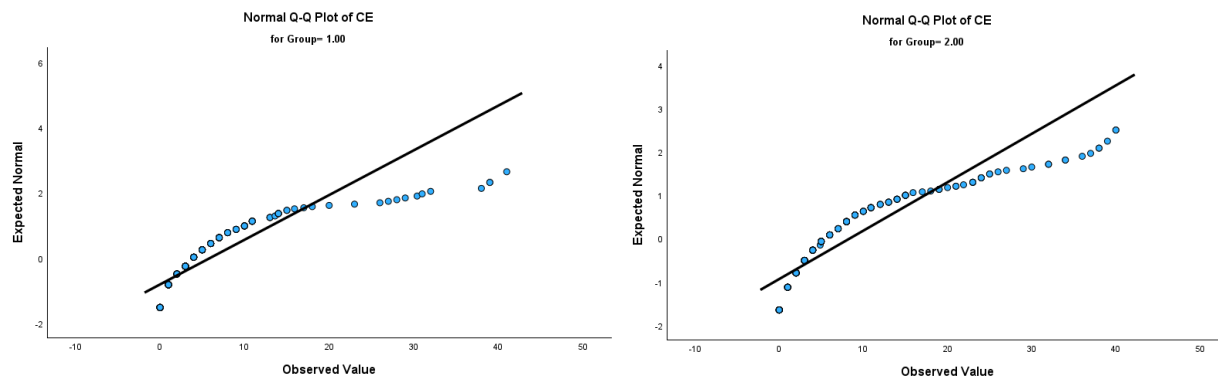


Note: mRt = mean reaction time, Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high Factor I motor impulsivity (FI-MI) treatment group.

Figure 32 shows Q-Q Plots (Quantile-Quantile Plots) for CE in the GNG task for both Group 1 (the control, low BIS-11 FI motor impulsivity group) and Group 2 (the treatment, high FI-MI group). The diagonal line represents a putative normal distribution. Both groups also show a platykurtic distribution demonstrating lightly tailed CE data and relatively few outliers.

Figure 32

Q-Q Plots of Treatment and Control Groups for CE for the GNG Model



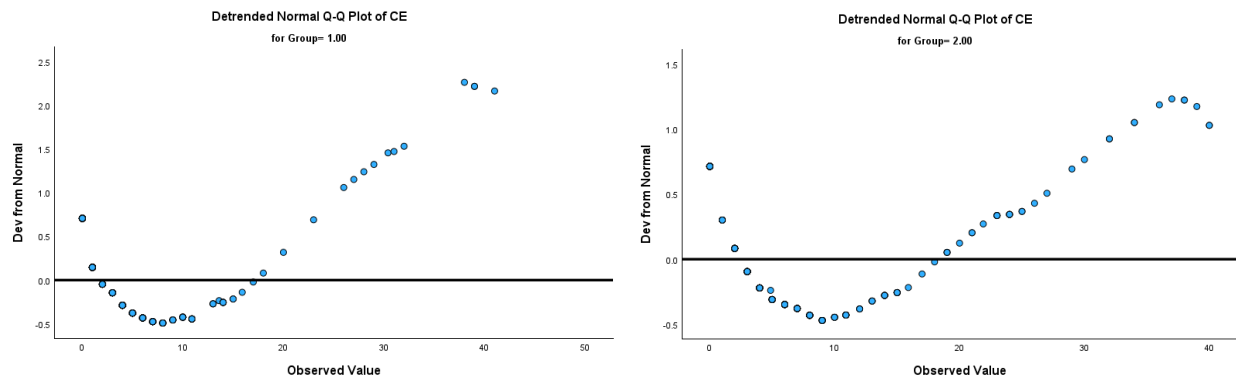
Note: CE = commission errors, Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high Factor I motor impulsivity (FI-MI) treatment group.

Figure 33 shows a detrended (extracting any reference to mean and variance) normal Q-Q plot of CE for the GNG task which shows the residuals (quantile delimited on y-axis) between observed and expected normal CE values (millisecond values on x-axis) for each of the control

(low FI-MI) and treatment (high FI-MI) groups. Both plots demonstrate positively skewed tailed distributions.

Figure 33

Detrended Normal Q-Q Plot of CE for the GNG Model

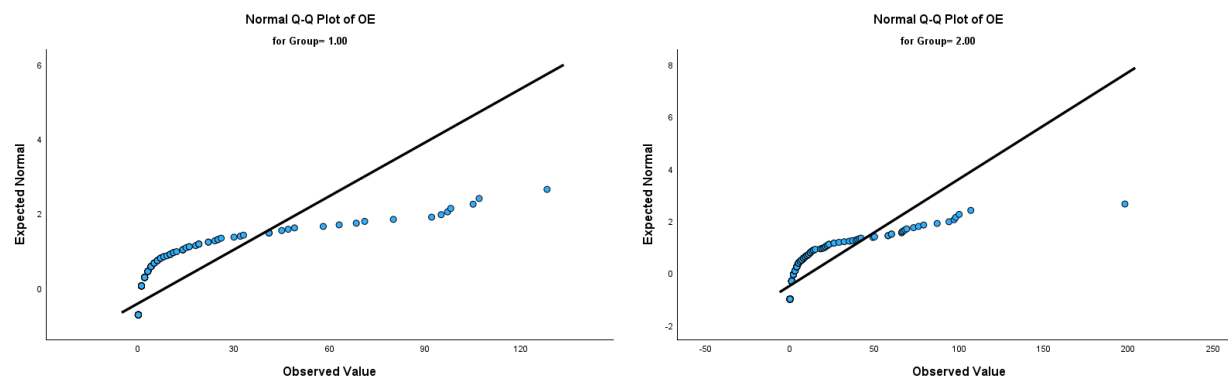


Note: CE = commission errors, Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high Factor I motor impulsivity (FI-MI) treatment group.

Figure 34 shows Q-Q Plots (Quantile-Quantile Plots) for OE for the GNG task for both Group 1 (the control, low BIS-11 FI motor impulsivity group) and Group 2 (the treatment, high FI-MI group). Both groups also show a platykurtic distribution demonstrating lightly tailed OE data and relatively few outliers.

Figure 34

Q-Q Plots of Treatment and Control Groups for OE for the GNG Model

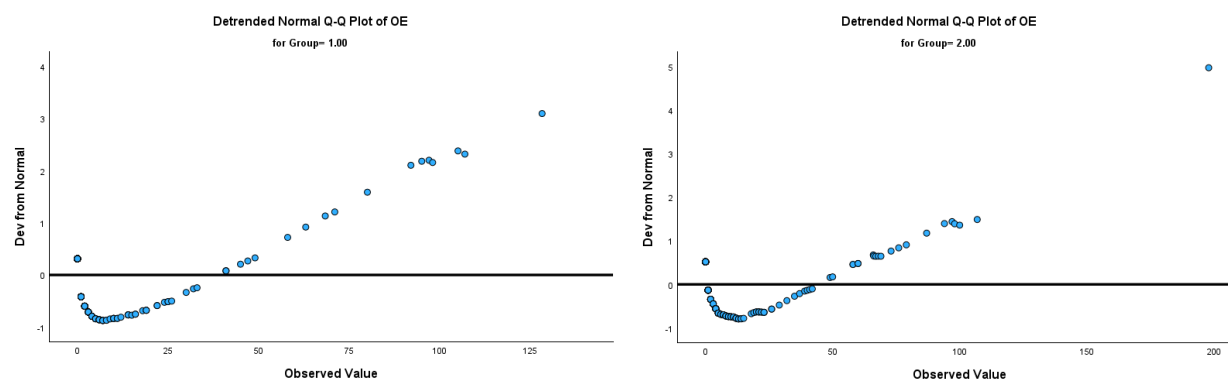


Note: CE = omission errors, Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high Factor I motor impulsivity (FI-MI) treatment group.

Figure 35 shows a detrended normal Q-Q plot of OE for the GNG task which shows the residuals (quantile delimited on y-axis) between observed and expected normal OE values (millisecond values on x-axis) for each of the control (low FI-MI) and treatment (high FI-MI) groups. Both plots demonstrate positively skewed tailed distributions.

Figure 35

Detrended Normal Q-Q Plot of OE for the GNG Model

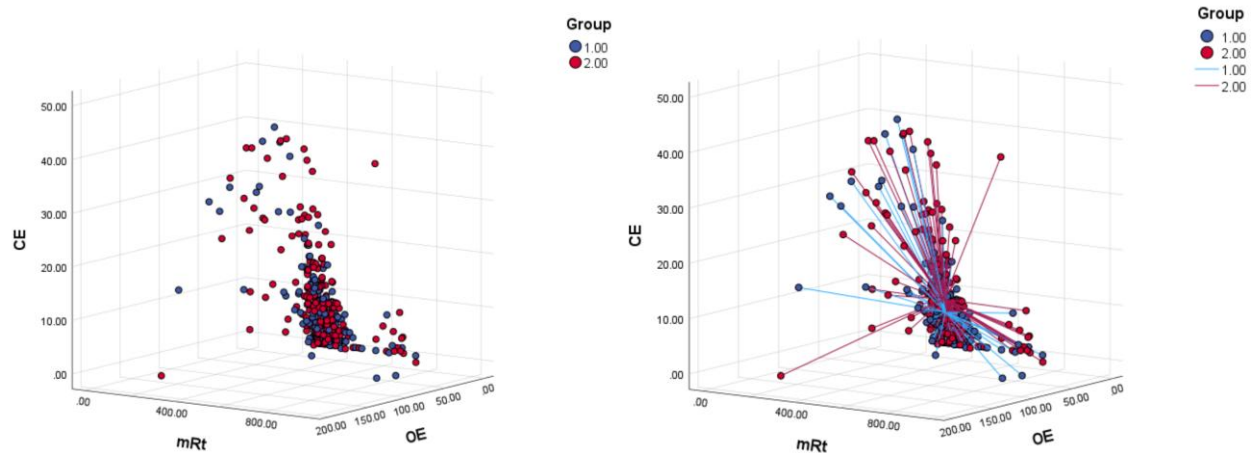


Note: CE = omission errors, Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high Factor I motor impulsivity (FI-MI) treatment group.

Figure 36 shows a three-dimensional scatter plot, with and without centroids, of the three dependent (outcome) variables of mRt, CE, and OE for the GNG model by independent (predictor) variable categorical group of low (Group 1) and high (Group 2) Factor I motor impulsivity (FI-MI) scores on the BIS-11. Figure 36 shows the interaction between the dependent (outcome) variables by group membership. The overlap in the cluster suggested that the groups did not significantly differ on the dependent variables, requiring more quantitative analysis via MANOVA and post hoc testing to tease out any statistically significant differences. The treatment group did appear to have more variability than the control group, which suggested some difference. In combination with centroids, the high FI-MI (treatment) group appeared to have higher commission errors (CE; false response when no response was necessary), higher mean reaction time (mRt; faster less controlled reaction times), and lower more tightly clustered omission errors (OE). The plot suggested some linearity with somewhat of a L-shaped pattern, but it could not be assumed without more testing.

Figure 36

Three Dimensional Scatter Plot Matrix by H-FIMI and L-FIMI for The GNG Model

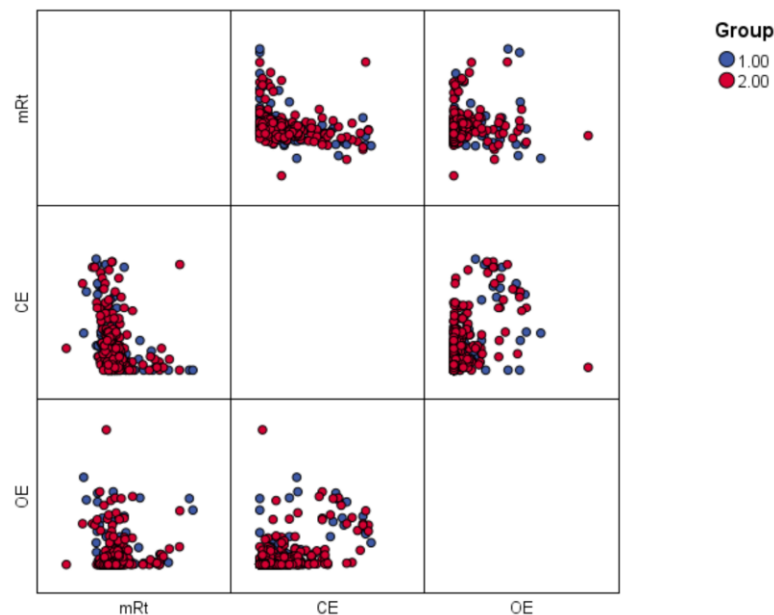


Note: mRt = mean reaction time, CE = commission errors, OE = omission errors. Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high Factor I motor impulsivity (FI-MI) treatment group.

Figure 37 shows a scatter plot matrix to illustrate the pairwise relationships between the three dependent (outcome) variables of mRt, CE, and OE for the GNG model. The scatter plot shows L-shaped patterns in the pairwise comparisons between mRt and CE for both Groups, with commission errors generally inversely proportional to mRt. As mRt increases, commission errors tend to decrease in frequency. This curvilinear pattern had implications for the linear assumptions underlying subsequent multivariate analyses and also suggested a curvilinear relationship between mRt and CE and thus, the presence of a reaction time threshold beyond which CE was significantly reduced. This is further explored next.

Figure 37

Scatterplot Matrix of mRt, CE, and OE for GNG Model



Note: mRt = mean reaction time, CE = commission errors, OE = omission errors. Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high Factor I motor impulsivity (FI-MI) treatment group.

Reaction Time Threshold Exploration

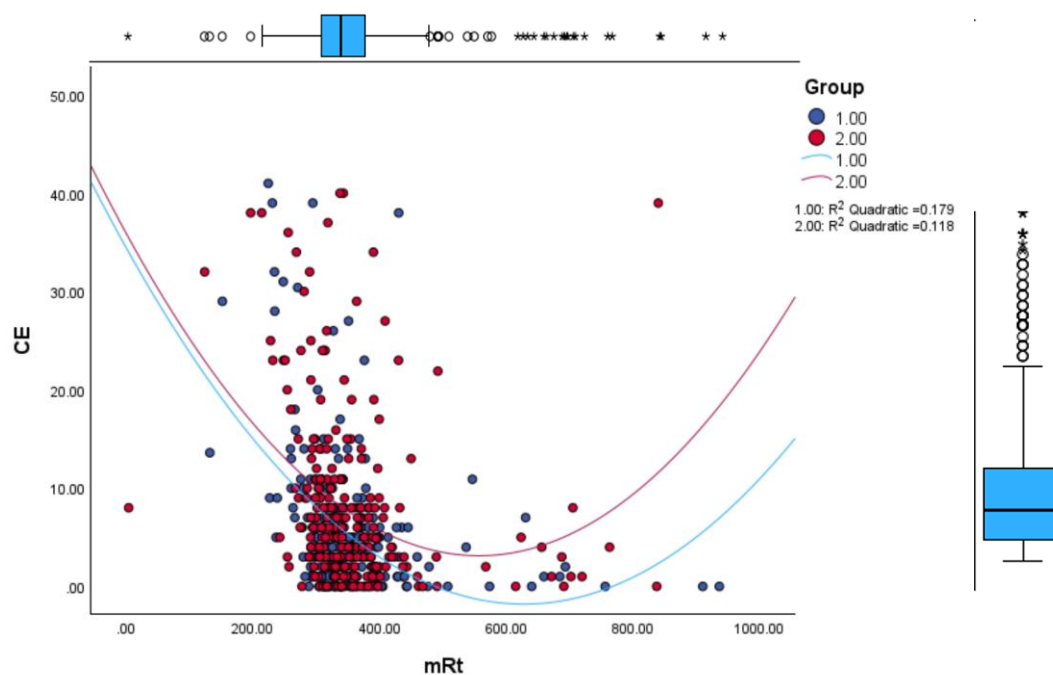
Figure 38 shows a regression variable plot with a quadratic option to visualize the curvilinear relationship and provide insight on a parabolic minima to localize the threshold of mRt that minimizes CE for each low MI (control Group 1) and high MI (treatment Group 2). Figure 38 includes box plots for each of mRt and CE to illustrate the primary range, outliers, and extreme outliers for each of these dependent (outcome) variables. The quadratic models show moderate explanatory power with the coefficient of determination (explained variance / total variance or $1 - [\text{sum of residuals} / \text{total sum of squares}]$) R^2 values of .179 for the low FI-MI

control Group 1 and .118 for the high FI-MI treatment group. This indicates that reaction time accounts for a reasonable portion of commission error variance (17.9% for the control group and 11.8% for the treatment group), though other factors clearly influence inhibitory control (BRI) performance.

The curve estimation shows a minima for the treatment (high FI-MI) group between 550 – 600 milliseconds. The minima for the control (low FI-MI) group passes through the origin and occurs at or above 600 milliseconds. Exact minima (representing the reaction time threshold at which commission errors are minimized) required a separate regression analysis on each group for mRt and CE, which were performed next (exact minima can also be calculated using the first and second derivative tests in calculus, Newton's method, or gradient descent from machine learning). The results of the subsequent regressions indicated that the optimal threshold for the control group is 625 milliseconds, which is 67 milliseconds longer than the treatment group threshold of 558 milliseconds. This finding suggests that individuals with high BIS-11 Factor I motor impulsivity reach their optimal speed-accuracy trade-off at faster reaction times, aligning with theoretical expectations that impulsive individuals achieve their best inhibitory control performance through quicker responding.

Figure 38

Quadratic Regression Variable Plot of CE vs. mRt for the GNG Model

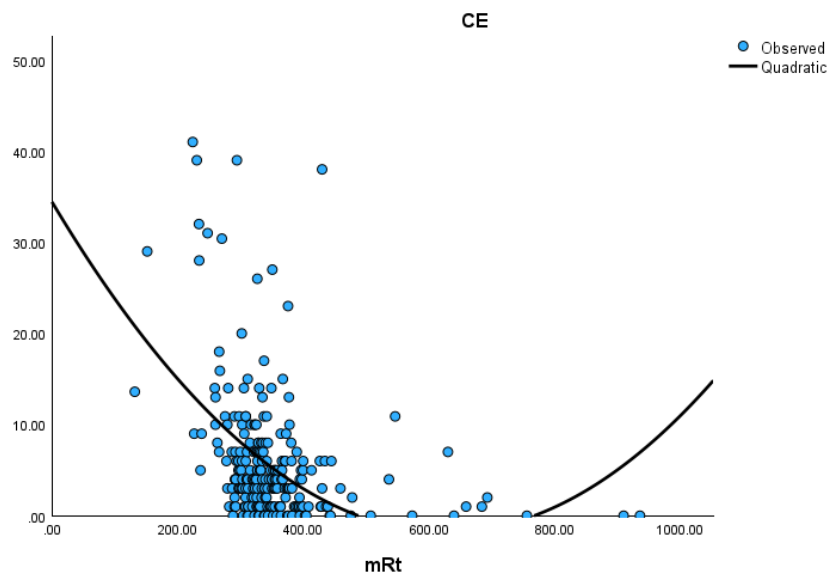


Note: mRt = mean reaction time, CE = commission errors; Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high Factor I motor impulsivity (FI-MI) treatment group.

Figure 39 shows the plot of the first quadratic regression model for the control (low MI) group of mRt as a predictor of CE. The results are evaluated using the regression calculations that follow.

Figure 39

Quadratic Regression Plot of mRt as Predictor of CE for Control Group of GNG Model



Note: mRt = mean reaction time, CE = commission errors; Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high Factor I motor impulsivity (FI-MI) treatment group.

Table 37 shows the first quadratic regression analysis (on the control Group 1, low FI-MI) that was conducted to examine the relationship between mean reaction time (mRt) and commission errors (CE) for each group (low and high motor impulsivity). The quadratic model was chosen to capture curvilinear trends in the data and identify the threshold and whether the relationship between mRt and CE differed between low and high Factor 1 BIS-11 motor impulsivity groups. The multiple correlation coefficient, $R = .423$, suggested a moderate correlation between mRt (the independent predictor variable in this model) and CE (the dependent outcome variable in this model). The coefficient of determination, $R^2 = .179$, indicates

17.9% of the variance in CE is explained by mRt and its quadratic term (mRt^2). Adjusting for the number of predictors in the model (adjusted $R^2 = .172$) indicates that the model was not subject to overfitting by adding a quadratic term.

Table 37

Quadratic Regression Model Summary for Control (Group 1) of mRt vs. CE for the GNG Model

<i>R</i>	<i>R</i> ²	Adjusted <i>R</i> ²	Std. Error of the
			Estimate
.423	.179	.172	6.645

Note: The independent variable is mRt.

Table 38 shows a table of the analysis of variance (ANOVA) results for the control group test and illustrate the overall model fit between mRt (independent predictor variable) and CE (dependent outcome variable). The table shows that mRt and its quadratic, $F[2, N-1] = 25.778$, significantly predicts CE, $p < .001$, in the control group.

Table 38

ANOVA table for Control Group 1 mRt vs. CE for the GNG Model

	<i>SS</i>	<i>df</i>	Mean Square	<i>F</i>	<i>p</i>
Regression	2276.440	2	1138.220	25.778	<.001
Residual	10464.726	237	44.155		
Total	12741.166	239			

Note: The independent variable is mRt.

Table 39 shows the coefficients of the quadratic regression between mRt (IV) and CE (DV) for the control (low FI-MI) group. The table provides the regression values per the following formula:

$$CE = \beta_0 + (\beta_1 \cdot mRt) + (\beta_2 \cdot mRt^2) \quad (35)$$

where β_0 is the intercept. $\beta_1, B_1 = -.115, p < .001$, for mRt and $\beta_2, B_2 = 9.201E-5, p < .001$, for mRt^2 indicate that as mRt increases, CE decreases until a threshold (minima) defined by a U-shaped parabolic curve above which CE increases again. The minima can be calculated using the equation

$$\chi_{min} = \frac{-\beta_1}{2\beta_2}$$

which yields a minima of 625.1 milliseconds, representing the threshold of mRt for CE for the control group.

Table 39

Coefficients of Quadratic Regression of mRt as Predictor of CE in the GNG Model (Control)

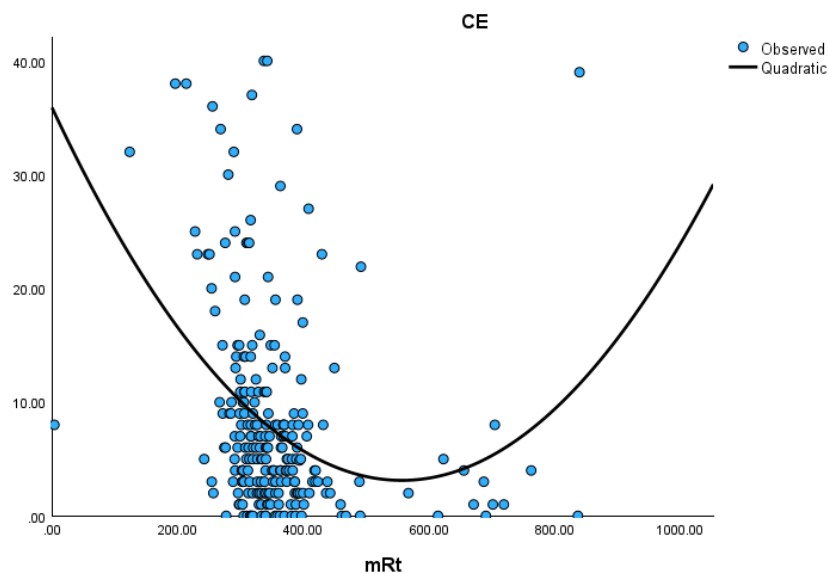
	Unstandardized Coefficients		Standardized Coefficients		
	<i>B</i>	Std. Error	β	<i>t</i>	<i>p</i>
mRt	-.115	.020	-1.471	-5.905	<.001
mRt ²	9.201E-5	.000	1.189	4.772	<.001
(Constant)	34.428	4.467		7.707	<.001

Note: mRt = mean reaction time.

Figure 40 shows the plot of the second quadratic regression model for the treatment (high FI-MI) group of mRt as a predictor of CE. The results are evaluated using the regression calculations that follow.

Figure 40

Quadratic Regression Plot of mRt as Predictor of CE for Treatment Group of the GNG Model



Note: mRt = mean reaction time, CE = commission errors; Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high Factor I motor impulsivity (FI-MI) treatment group.

Table 40 shows the second quadratic regression analysis (on the treatment Group 2, high FI-MI) that was conducted to examine the relationship between mean reaction time (mRt) and commission errors (CE) for each group (low and high motor impulsivity). As discussed above, the quadratic model was chosen to capture curvilinear trends in the data and identify the threshold and whether the relationship between mRt and CE differed between low and high

Factor I BIS-11 motor impulsivity groups. The multiple correlation coefficient, $R = .343$, also suggests a moderate correlation between mRt (the independent predictor variable in this model) and CE (the dependent outcome variable in this model). The coefficient of determination, $R^2 = .118$, indicates 11.8% of the variance in CE is explained by mRT and its quadratic term (mRt^2). Adjusting for the number of predictors in the model, adjusted $R^2 = .110$, indicates that the model was not subject to overfitting by adding a quadratic term. When comparing these results to the control (low FI-MI) results above, this suggests that mRt explains less variance in CE for the treatment (high FI-MI) group than for the control (low FI-MI) group, suggesting another factor contributes more significantly to CE variance in the treatment group versus the control group.

Table 40

Quadratic Regression Model Summary for Treatment (Group 2) of mRt vs. CE for the GNG Model

			Std. Error of the
R	R^2	Adjusted R^2	Estimate
.343	.118	.110	8.456

Note: The independent variable is mRt.

Table 41 shows a table of the analysis of variance (ANOVA) results to test and illustrate the overall model fit between mRt (independent predictor variable) and CE (dependent outcome variable). The table shows that mRt and its quadratic, $F[2, N-1] = 15.842$, significantly predicts CE, $p < .001$, although less so for the treatment (high FI-MI) group, than for the control (low FI-MI) group.

Table 41*ANOVA table for Treatment Group mRt vs. CE for the GNG Model*

	<i>SS</i>	<i>df</i>	Mean Square	<i>F</i>	<i>p</i>
Regression	2265.698	2	1132.849	15.842	<.001
Residual	16948.037	237	71.511		
Total	19213.735	239			

Note: The independent variable is mRt.

Table 42 shows the coefficients of the quadratic regression between mRt (IV) and CE (DV) for the treatment (high MI) group. As described above, the table provides the regression values per the following formula:

$$CE = \beta_0 + (\beta_1 \cdot mRt) + (\beta_2 \cdot mRt^2) \quad (37)$$

where β_0 is the intercept. $\beta_1, B_1 = -.118, p < .001$, for mRt and $\beta_2, B_2 = .000, p < .001$, for mRt^2 suggested a linear relationship rather than a curvilinear one because the coefficient for mRt^2 was zero, suggesting that the quadratic did not contribute to this regression model. However, both Figure 40 and significant t values for mRt, $t = -5.078$, and mRt^2 , $t = 4.364$, suggested a curvilinear model. Thus, B^2 could not equal zero, but must have been some positive number and SPSS may have been rounding the number down to zero. Expanding the significant figures in the SPSS output file bearded that out ($B_2 = .000105779927596, p < .001$). Therefore, this did suggest that as mRt increases, CE decreases until a threshold (minima) defined by a U-shaped parabolic curve above which CE increases again. As discussed previously, the minima can be calculated using the equation

(38)

$$\chi_{min} = \frac{-\beta_1}{2\beta_2}$$

which yielded a minima of approximately 558 milliseconds representing the threshold of mRt for CE for the treatment group.

Table 42

Coefficients of Quadratic Regression of mRt as Predictor of CE in GNG Model (Treatment)

	Unstandardized Coefficients		Standardized Coefficients	<i>t</i>	<i>p</i>
	<i>B</i>	Std. Error	β		
mRt	-.118	.023	-1.317	-5.078	<.001
mRt ²	.000	.000	1.132	4.364	<.001
(Constant)	35.894	5.134		6.992	<.001

Note: The independent variable is mRt.

Results For Hypothesis 2, RQ 2, GNG Model

A one-way (one-factor) between-subjects unpaired multivariate analysis of variance (MANOVA) was conducted to examine the effect of the dichotomous (categorical) independent predictor variable groupings (factor levels) of top and bottom quartile Factor I (FI) motor impulsivity (MI) scores on the BIS-11 on three dependent (outcome) variables of mean reaction time (mRt, in milliseconds), commission errors (CE), and omission errors (OE) of the go/no-go (GNG) laboratory behavioral task (measure). Analysis of the MANOVA results in SPSS-29

revealed a statistically significant (small-to-moderate) effect of BIS-11 FI motor impulsivity (MI) dichotomous independent (predictor) variable group (low MI [control] vs. high MI [treatment]) on the linear combination (variate) of the dependent (outcome) variables of mRt, CE, and OE, $F(1, 476) = 4.282, p = .005$, partial $\eta^2 = .026$. Univariate tests revealed a significant (large) effect for CE, $F(1, 476) = 10.587, p = .001$, partial $\eta^2 = .22$, indicating that individuals in the high FI-MI group committed significantly more commission errors than those in the low FI-MI group. However, no significant effects were found for mRt, $F(1, 476) = .305, p = .581$, partial $\eta^2 = .001$; or OE, $F(1, 476) = 2.462, p = .117$, partial $\eta^2 = .005$. Post-hoc tests of pairwise comparisons with Bonferroni correction, $SE = .746$, 95% CI [.962, 3.895], $p = .001$, and independent samples t -test via Welch's t -test, $t(478) = -3.254, df = 459.162, p = .001$ [2-tailed], $MD = -2.429, SE = .746$, 95% CI[-3.895, -.962], indicated that the dependent (outcome) variable of commission errors (CE) was the source of significance for the MANOVA of the linear variate (combination) of the three dependent (outcome) variables of mRt, CE, and OE. Details of the multivariate, univariate, and post-hoc tests are discussed below.

Multivariate Tests for the GNG Model

Table 43 shows the results of the multivariate tests for the GNG model (Hypothesis 2) for the intercept of the GNG model and for the group variable. As mentioned previously, because the homogeneity of covariances assumption was violated, Pillai's Trace was more appropriate to determine the effect size of variance in the dependent outcome variables as explained by the independent predictor variable. Pillai's trace is also less sensitive to violations of the MANOVA assumptions. Pillai's trace, $V = .026, F(3,476) = 4.282, p = .005$, indicated that the differences between the control (low BIS-11 FI motor impulsivity) and treatment (high FI-MI) groups were statistically significant. The effect size was small to moderate, however, partial $\eta^2 = .026$.

Comparison with other measures confirmed a small to moderate, but significant, effect. Wilk's Lambda (the proportion of variance of the dependent outcome variables that was not explained by the independent predictor variable) showed a small to moderate effect, $\Lambda = 0.974$, $p = 0.005$, partial $\eta^2 = 0.026$; Hotelling's Trace, $T^2 = .027$, $p = .005$, partial $\eta^2 = .026$, also showed a small to moderate effect as did Roy's Largest Root, $\theta = .027$, $p < .005$, partial $\eta^2 = .026$. As discussed in Chapter 3, since there is only one linear variate (and one eigenvector and eigenvalue) due to the model (research question) containing only one independent predictor variable (factor) and two levels (groups) for each independent variable, it was expected that the differences between the different calculations of the approximate F statistic would be similar. F values (statistic), $F = 4.282$, support statistical significance and small to moderate group differences via the ratio of systematic variance to error variance.

The observed power of .863 indicates that there is an 86.3% chance of finding the observed effect to be statistically significant in the sample of 480 participants. Consequently, the null hypothesis (H_o) for Hypothesis 1 of Research Question 1 (RQ1) was rejected on that basis as at least one dependent outcome variable differed between the two groups. As mentioned in Chapter 3, post-hoc analysis was required to determine which one or which combination of dependent variables accounted for the difference, although univariate tests did provide some preliminary indicators.

Table 43*Multivariate Tests for the GNG Model*

Effect	Value	Hypoth.				Parti	Noncent.	Observed
		F	df	Error df	p	al η^2	Parameter	Power ^c
Intercept								
Pillai's V	.948	2880.404 ^b	3.000	476.000	<.001	.948	8641.211	1.000
Wilks' Λ	.052	2880.404 ^b	3.000	476.000	<.001	.948	8641.211	1.000
Hotelling's T^2	18.154	2880.404 ^b	3.000	476.000	<.001	.948	8641.211	1.000
Roy's θ	18.154	2880.404 ^b	3.000	476.000	<.001	.948	8641.211	1.000
Group								
Pillai's V	.026	4.282 ^b	3.000	476.000	.005	.026	12.847	.863
Wilks' Λ	.974	4.282 ^b	3.000	476.000	.005	.026	12.847	.863
Hotelling's T^2	.027	4.282 ^b	3.000	476.000	.005	.026	12.847	.863
Roy's θ	.027	4.282 ^b	3.000	476.000	.005	.026	12.847	.863

^a Design: Intercept + Group. ^b Exact statistic, ^c Computed using $\alpha = .05$.

Univariate Tests Used to Build the MANOVA Model for the GNG and Identify Source of Difference

Table 44 shows the results of Levene's Test for Equality of Variances for each of the dependent (outcome) variables of mRt, CE, and OE. Using mean as the basis, the assumption of homogeneity of variance (homoscedasticity) was met for mRt, $F(1, 476) = .940, p = .333$, and OE, $F(1, 476) = 2.985, p = .085$, but not for CE, $F(1, 476) = 10.901, p = .001$. This heteroscedasticity outcome suggests an adjustment for post hoc testing for CE. Welch's *t*-test

(which is robust to differences in variance and adjusts for unequal group variances) would be preferred over the independent samples (Student's) *t*-test for CE (Delacre et al., 2017; Field, 2024; Ruxton, 2006; Tabachnick & Fidell, 2013).

Table 44

Levene's Test of Equality of Error Variances^a for the GNG Model

	Levene's <i>F</i>	<i>df1</i>	<i>df2</i>	<i>p</i>
mRt				
Based on Mean	0.940	1	478	.333
Based on Median	0.841	1	478	.360
Based on Median and with adjusted <i>df</i>	0.841	1	476.836	.360
Based on trimmed mean	0.892	1	478	.345
CE				
Based on Mean	10.901	1	478	.001
Based on Median	6.874	1	478	.009
Based on Median and with adjusted <i>df</i>	6.874	1	461.612	.009
Based on trimmed mean	9.457	1	478	.002
OE				
Based on Mean	2.985	1	478	.085
Based on Median	1.951	1	478	.163

	Levene's F	$df1$	$df2$	p
Based on Median and with adjusted df	1.951	1	467.696	.163
Based on trimmed mean	2.926	1	478	.088

Note: Tests the null hypothesis that the error variance of the dependent variable is equal across groups. mRt = mean reaction time, CE = commission errors, OE = omission errors.

^a Design: Intercept + Group

Table 45 shows the results of tests of between-subject effects via the univariate F s (separate univariate ANOVAs) for each dependent (outcome) variable of mRt, CE, and OE. This test informs determination of statistically significant differences between the two predictor groups (treatment, high FI-MI, or control, low FI-MI) on each individual dependent (outcome) variable. The results for the model sum of squares for the groups showed no statistically significant differences between groups for mRt, $F = .305$, $p = .581$, partial $\eta^2 = .001$, and OE, $F = 2.462$, $p = .117$, partial $\eta^2 = .005$, and a statistically significant difference between groups for CE with small to moderate effect, $F = 10.587$, $p = .001$, partial $\eta^2 = .022$. However, as noted above, CE violated the assumption of homogeneity of variance (homoscedasticity). Consequently, the noted significance above was not dispositive without adjusted post hoc testing or applying a transform (likely a log transform) to the data, at least for CE, or using a nonparametric test. The corrected model shows the total sums of squares, which demonstrates how much variance is explained by all predictors (independent variable factor levels) in the GNG model. Values for the corrected models were identical to the group model because there were no covariates in the model so the corrected model was simply the effect of group plus the intercept.

Table 45*Tests of Between-Subjects Effects for the GNG Model*

Source	DV	Type III Sum of Squares	<i>df</i>	Mean Square	<i>F</i>	<i>p</i>	partial η^2	Noncent. Parameter	Observed Power ^d
Corrected Model									
	mRt	2853.484 ^a	1	2853.484	0.305	.581	.001	0.305	.085
	CE	707.786 ^b	1	707.786	10.587	.001	.022	10.587	.901
	OE	1272.803 ^c	1	1272.803	2.462	.117	.005	2.462	.347
Intercept									
	mRt	60509985.637	1	60509985.637	6471.112	<.001	.931	6471.112	1.000
	CE	24596.749	1	24596.749	367.932	<.001	.435	367.932	1.000
	OE	50680.205	1	50680.205	98.025	<.001	.170	98.025	1.000
Group									
	mRt	2853.484	1	2853.484	0.305	.581	.001	0.305	.085
	CE	707.786	1	707.786	10.587	.001	.022	10.587	.901
	OE	1272.803	1	1272.803	2.462	.117	.005	2.462	.347
Error									
	mRt	4469675.952	478	9350.787					
	CE	31954.901	478	66.851					
	OE	247132.437	478	517.013					
Total									
	mRt	64982515.073	480						

Source	DV	Type III Sum of			<i>F</i>	<i>p</i>	η^2	partial Noncent. Parameter	Observed Power ^d
		Squares	<i>df</i>	Mean Square					
	CE	57259.436	480						
	OE	299085.445	480						
Corrected Total									
	mRt	4472529.436	479						
	CE	32662.687	479						
	OE	248405.240	479						

Note: mRt = mean reaction time, CE = commission errors, OE = omission errors.

^a $R^2 = .001$ (Adjusted $R^2 = -.001$). ^b $R^2 = .022$ (Adjusted $R^2 = .020$). ^c $R^2 = .005$ (Adjusted $R^2 = .003$). ^d Computed using $\alpha = .05$

Table 46 shows parameter estimates for GNG (Hypothesis 2) for each dependent (outcome) variable of mRt, CE, and OE. In this study, parameter estimates were not necessary because there were no covariates, although parameter estimates can be useful for determining the magnitude and direction of effects of the independent (predictor) variable on the dependent (outcome) variables as well as test, confirm, or support interpretation of main effects, Levene's test, and tests of between-subject effects via univariate *F*s (Field, 2024; George & Mallery, 2024). There was no statistically significant result for mRt, $B = -4.867$, $p = .581$, and partial $\eta^2 = 0.001$, or for OE, $B = -3.257$, $p = .117$, partial $\eta^2 = 0.005$. There was a statistically significant result for CE with a large effect, $B = -2.429$, $p = .001$, partial $\eta^2 = 0.22$, which is consistent with the other tests. The *B* statistic is negative because SPSS-29 sets the first numerical category (the

low FI-MI control group in this case) as the reference group and, as such, the statistics are relative to the other group (the high FI-MI treatment group), which is set at zero.

Table 46

Parameter Estimates for the GNG Model

		95% Confidence								
			Std.			Interval		partial	Noncent.	Observed
DV	Parameter	<i>B</i>	Error	<i>t</i>	<i>p</i>	Lower	Upper	η ²	Parameter	Power ^b
mRt										
	Intercept	357.491	6.242	57.273	<.001	345.226	369.756	.873	57.273	1.000
	[Group=1.00]	-4.876	8.827	-0.552	.581	-22.222	12.469	.001	0.552	.085
	[Group=2.00]	0 ^a	.	.	.	.	.	.	.	.
CE										
	Intercept	8.373	.528	15.864	<.001	7.336	9.410	.345	15.864	1.000
	[Group=1.00]	-2.429	.746	-3.254	.001	-3.895	-0.962	.022	3.254	.901
	[Group=2.00]	0 ^a	.	.	.	.	.	.	.	.
OE										
	Intercept	11.904	1.468	8.110	<.001	9.020	14.788	.121	8.110	1.000
	[Group=1.00]	-3.257	2.076	-1.569	.117	-7.335	0.822	.005	1.569	.347
	[Group=2.00]	0 ^a	.	.	.	.	.	.	.	.

Note: mRt = mean reaction time, CE = commission errors, OE = omission errors.

^a This parameter is set to zero because it is redundant. ^b Computed using $\alpha = .05$

Table 47 shows the between-subjects sum of squares cross product (SSCP) matrices of the GNG model. The SSCP matrices are foundational precursors to calculation of eigenvalues for the F statistic and used to explore the pattern of the data via cross-products (uncentered covariance matrix) to characterize the relationship (covariability) between the dependent (outcome) variables of mRt, CE, and OE. As noted in Chapter 3's discussion of MANOVA mathematics, the SSCP is calculated in MANOVA, after extracting the eigenvalue from the eigenvector for each dependent (outcome) variable, via least squares regression to calculate the sum of squares. Then, MANOVA calculates the sum of squares of the error (within groups unsystematic residual variance) and then total sum of squares. Next, MANOVA calculates the sum of the cross-product covariance (via matrix and linear algebra) and finally the SSCP matrices. SSCP matrices thus enable MANOVA to consider cross correlations between the dependent (outcome) variables, which ANOVAs cannot do.

The hypothesis intercept matrix in Table 47 provides the total variability of the model resulting primarily from the intercept. The group matrix in Table 47 provides the sum of squares and cross product (SSCP) output to characterize the effect of the independent (predictor) variable of FI-MI (high and low groups) on group differences of the dependent (outcome) variables. The error matrix in Table 47 provides the residual variance in light of group differences. The group diagonals represent the sum of squares (SS) and the off-diagonals represent the cross-products (CP). Thus, the diagonals ($mRt = 2853.484$, $CE = 707.786$, $OE = 1272.803$) show the magnitude of how much variance each dependent (outcome) variable contributes to the group difference. The largest explained variance is for CE (707.786), supporting the previous observations regarding the effect of the CE dependent (outcome) variable. Positive off-diagonals indicate a positive relationship (correlation).

The within group error matrix represents unexplained variability in the model. The diagonal for mRt, CE, and OE contains large values indicating a very high variance (determinants) in mRt, very high variance for OE, and high variance for CE. Off-diagonal values (45,442.616) for CE and OE suggested correlation between the two, whereas a negative covariance (-97,858.201) between mRt and CE suggested an inverse (orthogonal) relationship. Because the error variance was significantly higher than the group variance, the SSCP matrices supported the previous indicators that CE was driving the significance of group differences, whereas OE and mRt were not significantly affected by group differences.

Table 47

Between-Subjects SSCP Matrix for GNG Model

		mRt	CE	OE
Hypothesis				
	Intercept			
	mRt	60509985.637	1219979.073	1751187.726
	CE	1219979.073	24596.749	35306.774
	OE	1751187.726	35306.774	50680.205
	Group			
	mRt	2853.484	1421.146	1905.760
	CE	1421.146	707.786	949.143
	OE	1905.760	949.143	1272.803
Error				
	mRt	4469675.952	-97858.201	73777.215

	mRt	CE	OE
CE	-97858.201	31954.901	45442.616
OE	73777.215	45442.616	247132.437

Note: Based on Type III Sum of Squares. mRt = mean reaction time, CE = commission errors, OE = omission errors.

Table 48 shows the residual SSCP matrices for the GNG model. It contains the variance-covariance (mean sum of squares-mean cross product) matrix (mean form of the SSCP matrix) and the correlation matrix. As described in Chapter 3, this measure interrogates any error (unexplained variance [discriminant]) and covariances after fitting the model (GNG model in this case).

Starting with the correlation matrix, the diagonals of unity represent perfect self-variable correlation and off-diagonals characterize the direction and strength of relationships among the three dependent (outcome) variables of mRt, CE, and OE. Standardizing the covariance matrix here yielded Pearson correlation coefficients (r). The results indicated a positive correlation, $r = .511$, between CE and OE, a weak positive correlation, $r = .070$, between mRt and OE, and a negative correlation, $r = -.259$, between mRt and CE, which was consistent with prior observations. These results suggested that CE was more sensitive than OE to mRt with longer reaction times decreasing commission errors, although there was a moderately strong correlation between OE and CE, which implicated MANOVA assumptions. The diagonal of the residual SSCP matrix array contains high values (mRT = 4,469,675.952, CE = 31,954.901, OE = 247,132.37), suggesting significant residual variability. The negative off-diagonal values (-

97,858.201) for the cross-products of mRt and CE suggest that they covary. The covariance matrix off-diagonal values (-204.724) also supports covariance between mRt and CE.

Table 48

Residual SSCP Matrix for the GNG Model

	mRt	CE	OE
Sum-of-Squares and Cross-Products			
mRt	4469675.952	-97858.201	73777.215
CE	-97858.201	31954.901	45442.616
OE	73777.215	45442.616	247132.437
Covariance			
mRt	9350.787	-204.724	154.346
CE	-204.724	66.851	95.068
OE	154.346	95.068	517.013
Correlation			
mRt	1.000	-.259	.070
CE	-.259	1.000	.511
OE	.070	.511	1.000

Note: mRt = mean reaction time, CE = commission errors, OE = omission errors.

Table 49 shows the estimated marginal means describing the adjusted means for each dependent (outcome) variable of mRt, CE, and OE by dichotomous group (BIS-11 FI low MI [Group 1], and high FI-MI [Group 2]). The treatment group (high FI-MI) had higher commission errors, CE), $\bar{x} = 8.373$, $SE = .528$, than the control group (low FI-MI) $\bar{x} = 5.944$, $SE = 0.528$,

which, as previously reported, was significant, $p = .001$. The treatment group (high FI-MI) also had higher OE, $\bar{x} = 11.904$, $SE = 1.468$, than the control (low FI-MI) group, $\bar{x} = 8.647$, $SE = 1.468$, as well as higher mRt, $\bar{x} = 357.491$, $SE = 6.242$, for the treatment (high FI-MI) group than the control (low FI-MI) group, $\bar{x} = 352.615$, $SE = 6.242$, although neither difference was statistically significant, $p = .117$ and $p = .581$, respectively.

Table 49

Estimated Marginal Means for the GNG Model

DV	Group	$\bar{x}$	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
mRt	Control (L-FIMI)	352.615	6.242	340.350	364.880
	Treatment (H-FIMI)	357.491	6.242	345.226	369.756
CE	Control (L-FIMI)	5.944	0.528	4.907	6.981
	Treatment (H-FIMI)	8.373	0.528	7.336	9.410
OE	Control (L-FIMI)	8.647	1.468	5.763	11.531
	Treatment (H-FIMI)	11.904	1.468	9.020	14.788

Note: mRt = mean reaction time (ms); CE = commission errors; OE = omission errors. Group 1 = Low FI-MI (Control); Group 2 = High FI-MI (Treatment).

Post Hoc Tests for the GNG Model

Since the MANOVA results indicated statistical significance between groups on a linear variate (combination) of the three dependent (outcome) variables mRt, CE, and OE, post hoc tests were run to identify (confirm from univariate tests) the source of the difference. Table 50 shows post hoc tests of pairwise comparisons for the go/no-go (GNG) model. As applied to this

study, the tests of pairwise comparisons (with Bonferroni correction) comprise the practical equivalent of post MANOVA independent samples *t*-tests in cases where there is only one independent variable with two groups and pairwise comparisons test each group individually against each dependent variable. This is fundamentally similar to what independent samples *t*-tests do (independent samples *t*-tests were also run as described in Chapter 3 and are provided below pairwise comparisons). Consequently, pairwise comparisons examine the differences between the independent (predictive) variable dichotomous treatment (high BIS-11 FI motor impulsivity [MI]) and control (low FI-MI) groups on the three dependent (outcome) variables of mean reaction time (mRt), commission errors (CE), and omission errors (OE) for the GNG model.

The results of the pairwise comparisons in Table 50 showed that, of the three dependent (outcome) variables, CE was responsible for the statistical significance of the differences between the high FI-MI (treatment) and low FI-MI (control) groups. The treatment (high FI-MI) group (shown as Group 2 in Table 50) had a highly significant average of 2.429 greater number of commission errors (CE) than the control group (Group 1), $SE = .746$, 95% CI [.962, 3.895], $p = .001$. The mean reaction time (mRt) did not significantly contribute to group differences. The treatment (Group 2) group had an mRT, on average, that was an insignificant 4.876 milliseconds higher than control (Group 1) group, $SE = 8.827$, CI[-12.469, 22.222], $p = .581$. Omission errors (OE) also did not significantly contribute to group differences. The treatment (Group 2) group also committed, on average, a non-significant 3.257 greater omission errors than the control (Group 1) group, $SE = 2.076$, CI[-.822, 7.335], $p = .117$.

Table 50*Pairwise Comparisons for the GNG Model*

DV	(I) Group	(J) Group	95% Confidence Interval for				
			Mean	Std. Error	p^a	Difference ^b	
			Difference (I-J)			Lower Bound	Upper Bound
mRt	1	2	-4.876	8.827	.581	-22.222	12.469
	2	1	4.876	8.827	.581	-12.469	22.222
CE	1	2	-2.429*	0.746	.001	-3.895	-0.962
	2	1	2.429*	0.746	.001	0.962	3.895
OE	1	2	-3.257	2.076	.117	-7.335	0.822
	2	1	3.257	2.076	.117	-0.822	7.335

Note: Based on estimated marginal means. Mean differences represent Group 1 (Control low Factor I motor impulsivity [FI-MI]) minus Group 2 (Treatment high FI-MI). Negative values indicate higher scores in the Treatment group. mRt = mean reaction time, CE = commission errors; OE = omission errors.

^a $p < .05$ (significant), $p < .01$ (highly significant). ^b Adjustment for multiple comparisons: Bonferroni.

* The mean difference is significant at the .05 level.

Table 51 shows the independent samples t -test for the GNG model (Hypothesis 2) to identify which dependent variable was, or which variables were, responsible for the significance of the MANOVA results by comparing the means of the two groups for each dependent (outcome) variable. The results include statistics for equal variances assumed (EVA) and equal

variances not assumed (EVNA), the latter in case the equality of variances assumption (homoscedasticity assumption) was violated. As previously reported, Levene's Test for Equality of Variances (homoscedasticity assumption) was violated for CE (heteroscedasticity detected for CE), but not for mRt or OE. Consequently, EVNA, which represents Welch's t -test, was reported for CE, and EVA results, which represents the independent samples t -test, was reported for mRt and OE. Welch's t -test ignores the results (F statistic) from Levene's Test for Equality of Variances and adjusts the degrees of freedom by applying the Welch-Satterthwait equation below, which pools the degrees of freedom by taking an approximation of the effective degrees of freedom (df) of a linear variate (combination) of independent sample variances (Delacre et al., 2017; Ruxton, 2006). (39)

$$v_{\chi'} \approx \frac{(\sum_{i=1}^n k_i s_i^2)^2}{\sum_{i=1}^n \frac{(k_i s_i^2)^2}{v_i}}$$

Where $v_{\chi'}$ are the approximate (non-analytical) degrees of freedom, k reflects the number of components, and s_i the standard deviation of the i^{th} component. Since the degrees of freedom differed between the independent samples (Student's) t -test (and the sample sizes are the same between groups) and Welch's t -test, the t -value was identical, but the p -value differed between the two (Delacre et al., 2017).

The results indicated that only one dependent (outcome) variable, CE, was responsible for the significance of the MANOVA results, $p = .001$ [2-tailed]. Using EVNA, the t statistic for Welch's t -test (the mean difference for the two categorical predictor variables on CE divided by the standard error of the difference [essentially a signal to noise ratio]) was relatively large and the confidence interval did not cross zero, which supported statistical significance, $t(478) = -$

3.254, $df = 459.162$, $MD = -2.42863$, $SE = .74639$, 95% CI[-3.89523, -.96187]. Using EVA, neither mRt, $F(1,478) = .940$, $t(478) = -.552$, $p = .581$ [2-tailed], 95% CI[-22.22, 12.47], nor OE, $F(1,478) = 2.985$, $t(478) = -1.569$, $p = .117$ [2-tailed], 95% CI[-7.34, .82], had means that were significantly different between groups.

Table 51

Independent Samples T-tests for the GNG Model

Levene's										
Test		<i>t</i> -test for EOM								
						Significance	Mean	Std. Error	95% CIOD	
		<i>F</i>	<i>p</i>	<i>t</i>	<i>df</i>	1-Sid <i>p</i> 2-Sid <i>p</i>	Diff.	Diff.	Lower	Upper
mRt										
EVA	0.940	.333	-.552	478	.290	.581	-4.876	8.827	-22.222	12.469
EVNA			-.552	475.341	.290	.581	-4.876	8.827	-22.222	12.4692
CE										
EVA	10.901	.001	-3.254	478	<.001	.001	-2.429	0.746	-3.895	-.962
EVNA			-3.254	459.162	<.001	.001	-2.429	0.746	-3.895	-.962
OE										
EVA	2.985	.085	-1.569	478	.059	.117	-3.257	2.076	-7.335	0.822
EVNA			-1.569	466.340	.059	.117	-3.257	2.076	-7.336	0.822

Note: mRt = mean reaction time, CE = commission errors, OE = omission errors. EVA = equal variances assumed, EVNA = equal variances not assumed. COID = confidence interval of the difference. EOM = equality of means.

Table 52 shows the effect sizes for the independent samples for GNG. The effect size for CE demonstrated a small-to-moderate effect, Cohen's $d = -.297$, CI $[-.477, -.117]$, which was consistent with results of other tests previously described (supported by a confidence interval that did not include zero). The negative sign of the statistic indicated that the Factor I motor impulsivity BIS-11 values of the treatment (high) group had significantly more commission errors (CE) than the control (low) group. Neither mRt, Cohen's $d = -.050$, CI $[-.229, .129]$, or OE, Cohen's $d = -.143$, CI $[-.322, .036]$, demonstrated any statistically significant effects, also consistent with previous indicators. Consequently, the results of post hoc tests for sub-Research Questions RQ2a, RQ2b, and RQ2c supported rejection of the sub-null hypothesis $H2b_0$ and acceptance of the sub-alternate Hypothesis $H2b_A$, and acceptance of sub-null hypothesis $H2a_0$ and $H2c_0$, and rejection of sub-alternate Hypothesis $H2a_A$ and $H2c_A$.

Table 52

Independent Samples Effect Sizes for the GNG Model

				95% Confidence Interval	
		Standardizer ^a	Point Estimate	Lower	Upper
mRt	Cohen's d	96.699	-.050	-.229	.129
	Hedges' g	96.852	-.050	-.229	.128
	Glass's Δ	100.251	-.049	-.228	.130
CE	Cohen's d	8.176	-.297	-.477	-.117
	Hedges' g	8.189	-.297	-.476	-.117
	Glass's Δ	8.966	-.271	-.451	-.090
OE	Cohen's d	22.738	-.143	-.322	.036

	Standardizer ^a	Point Estimate	95% Confidence Interval	
			Lower	Upper
Hedges' <i>g</i>	22.774	-.143	-.322	.036
Glass's Δ	24.470	-.133	-.312	.046

Note: mRt = mean reaction time, CE = commission errors, OE = omission errors. a. The denominator used in estimating the effect sizes. Cohen's *d* uses the pooled standard deviation. Hedges' *g* uses the pooled standard deviation, plus a correction factor. Glass's Δ uses the sample standard deviation of the control (i.e., the second) group.

Research Question 3 (RQ3), H3, The Stop Signal Task (SST) Model

RQ3

Do linear variates of stop signal reaction time (SSRT), commission errors (CE), and omission errors (OE) in the stop-signal task (SST) differ between high and low motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults ages 18-40?

RQ3a. Is there a difference in stop signal reaction time (SSRT) in the SST between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40?

RQ3b. Is there a difference in commission errors (CE) in the SST between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40?

RQ3c. Is there a difference in omission errors (OE) in the SST between high and low motor impulsiveness subscale groups on the BIS-11 in adults ages 18-40?

H3₀ (Null Hypothesis)

Linear variates of stop signal reaction time (SSRT), commission errors (CE), and omission errors (OE) in the stop-signal task (SST) do not differ between high and low motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults ages 18-40.

H3_a

Linear variates of stop signal reaction time (SSRT), commission errors (CE), and omission errors (OE) in the stop-signal task (SST) differ between high and low motor impulsiveness subscale groups on the Barratt Impulsiveness Scale (BIS-11) in adults 18-40.

H3a₀. There is no difference in stop signal reaction time (SSRT) in the SST between high and low motor impulsiveness subscale groups on the BIS-11 in adults 18-40.

H3a_A. There is a difference in stop signal reaction time (SSRT) in the SST between high and low motor impulsiveness subscale groups on the BIS-11 in adults 18-40.

H3b₀. There is no difference in commission errors (CE) in the SST between high and low motor impulsiveness subscale groups on the BIS-11 in adults 18-40.

H3b_A. There is a difference in commission errors (CE) in the SST between high and low motor impulsiveness subscale groups on the BIS-11 in adults 18-40.

H3c₀. There is no difference in omission errors (OE) in the SST between high and low motor impulsiveness subscale groups on the BIS-11 in adults 18-40.

H3c_A. There is a difference in omission errors (OE) in the SST between high and low motor impulsiveness subscale groups on the BIS-11 in adults 18-40.

Validity and Reliability of the Data: Hypothesis 3: SST Model

The SST model demonstrated psychometric soundness consistent with the strong discriminant validity and test-retest reliability, SSRT $ICC = 0.72$, for the instrument discussed in

Chapter 3. The implementation of optimization criteria from recent literature discussed in Chapter 3, including the integration method for SSRT calculation, proved effective in detecting BIS-11 Factor I motor impulsivity group differences. The moderate positive correlations between stop signal reaction time (SSRT) and both commission errors (CE), $r = .501$, and omission errors (OE), $r = .484$, supported the instrument's internal structure and theoretical coherence. The sensitivity of SSRT to influential outliers, while requiring careful interpretation, aligned with the literature's recognition of implementation challenges discussed in Chapter 3 while confirming the measure's capacity to detect genuine inhibitory control differences.

Table 53 shows the tests for normality for the SST task study (Hypothesis 3). Considering the sample size (>50) the results of a Kolmogorov-Smirnov test were used to evaluate normality rather than the Shapiro-Wilk test, which is better for small sample sizes. None of the three dependent (outcome) variables for Research Question 3, Hypothesis 3 (SST) were normally distributed, $p < .001$, by this measure.

Table 53

Tests for Normality for the SST Model

		Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Group	Statistic	<i>df</i>	<i>p</i>	Statistic	<i>df</i>	<i>p</i>
SSRT	Trmt	.193	240	<.001	.763	240	<.001
	Cont	.205	240	<.001	.761	240	<.001
CE	Trmt	.156	240	<.001	.931	240	<.001
	Cont	.167	240	<.001	.918	240	<.001
OE	Trmt	.276	240	<.001	.635	240	<.001

Group	Kolmogorov-Smirnov ^a			Shapiro-Wilk		
	Statistic	<i>df</i>	<i>p</i>	Statistic	<i>df</i>	<i>p</i>
Cont	.312	240	<.001	.539	240	<.001

Note: SSRT = stop signal reaction time, CE = commission errors, OE = omission errors.

^a Lilliefors Significance Correction.

Table 54 shows descriptive statistics for the SST stop signal reaction time (SSRT) dependent (outcome) variable for each of the high (treatment) and low (control) BIS-11 Factor I motor impulsivity (FI-MI) groups. If tests for normality do not pass, skewness and kurtosis at or close to zero may indicate oversensitivity of normality tests due to a large sample size. Skewness for SSRT was high for both the low FI-MI - control (skewness = 2.312) and high FI-MI treatment (skewness = 2.207) groups, indicating a strongly positive (right tailed) distribution. Kurtosis was also high for control (kurtosis = 6.253) and treatment groups (kurtosis = 5.340) suggesting very heavy positive leptokurtic tails in the data, consistent with the results of the Kolmogorov-Smirnov test. Mean for SSRT was higher for the high FI-MI treatment group, $\bar{x}$ = 307.3 ms, than the low FI-MI control group, $\bar{x}$ = 269.2 ms. This suggested that the treatment group had measurably poorer behavioral response inhibition (slower inhibitory control) than the control group, so arguably members of the treatment group were, on average, more impulsive (i.e., had deficits in behavioral response inhibition [BRI]).

Table 54*Descriptive Statistics for SSRT for the SST Model*

		Control (Low FIMI)		Treatment (High FIMI)	
		Statistic	Std. Error	Statistic	Std. Error
SSRT					
$\bar{x}$		269.2	11.262	307.3	13.038
95% Confidence	Lower Bound	247.0		281.7	
Interval for Mean	Upper Bound	291.4		333.0	
5% Trimmed Mean		247.8		281.3	
Median (<i>Mdn</i>)		219.8		247.0	
Variance (s^2)		30441.5		40796.2	
Std. Deviation (<i>SD</i>)		174.5		202.0	
Minimum		39.0		74.0	
Maximum		1124.3		1162.0	
Range		1085.3		1088.0	
Interquartile Range (<i>IQR</i>)		126.1		156.6	
Skewness		2.312	.157	2.207	.157
Kurtosis		6.253	.313	5.340	.313

Note: SSRT = stop signal reaction time.

Table 55 shows descriptive statistics for the SST commission errors (CE) dependent (outcome) variable for each of the low (control) and high (treatment) BIS-11 Factor I motor impulsivity groups. Skewness for CE was slightly higher for the control (skewness = 1.002) than

treatment (skewness = 0.929) groups, indicating a moderately positive distribution. Kurtosis was also high for control (kurtosis = 0.994) and treatment (kurtosis = 0.712) suggesting nearly normal distribution with slightly positive tails in the data. Mean for the treatment (high FI-MI) group, $\bar{x} = 27.7$, was not significantly different from the mean for the control (low FI-MI) group, $\bar{x} = 27.3$. This mitigates the violation of normality in the test for normality above.

Table 55

Descriptive Statistics of CE for the SST Model

	Control (Low FIMI)		Treatment (High FIMI)	
	Statistic	Std. Error	Statistic	Std. Error
CE				
$\bar{x}$	27.3	.288	27.7	.304
95% Confidence Interval for Lower Bound	26.8		27.0	
Mean	Upper Bound	27.9	28.2	
5% Trimmed Mean	27.1		27.4	
Median (<i>Mdn</i>)	26.0		27.0	
Variance (s^2)	19.9		22.2	
Std. Deviation (<i>SD</i>)	4.5		4.7	
Minimum	18.0		17.0	
Maximum	41.0		42.0	
Range	23.0		25.0	
Interquartile Range (<i>IQR</i>)	4.0		5.0	
Skewness	1.002	.157	0.929	.157

	Control (Low FIMI)		Treatment (High FIMI)	
	Statistic	Std. Error	Statistic	Std. Error
Kurtosis	0.994	.313	0.712	.313

Note: CE = commission errors.

Table 56 shows descriptive statistics for the SST omission errors (OE) dependent (outcome) variable for each of the high (treatment) and low (control) BIS-11 Factor I motor impulsivity groups. The treatment group (high FI-MI) had higher OE, $\bar{x} = 10.7$, than the control group (low FI-MI), $\bar{x} = 8.8$, suggesting poorer inhibitory control, on average, for members of the treatment group. Skewness for OE was high for both the control (skewness = 3.334) and treatment (skewness = 2.529) groups, indicating a strongly positive distribution. Kurtosis was also high for control (kurtosis = 12.779) and treatment (kurtosis = 6.752), more so than CE, suggesting very heavy leptokurtic positive tails in the data.

Table 56

Descriptive Statistics of OE for the SST Model

	Treatment			
	Control (Low FI-MI)		(High FI-MI)	
	Statistic	Std. Error	Statistic	Std. Error
OE				
$\bar{x}$	8.8	1.155	10.7	1.163
Lower Bound	6.5		8.4	

		Treatment			
		Control (Low FI-MI)		(High FI-MI)	
		Statistic	Std. Error	Statistic	Std. Error
95% Confidence Interval	Upper Bound	11.1		13.0	
for Mean					
5% Trimmed Mean		5.7		7.9	
Median (<i>Mdn</i>)		2.0		3.0	
Variance (s^2)		320.4		324.3	
Std. Deviation (<i>SD</i>)		17.9		18.0	
Minimum		0.00		0.00	
Maximum		117.0		104.00	
Range		117.0		104.00	
Interquartile Range (<i>IQR</i>)		7.8		9.0	
Skewness		3.334	.157	2.529	.157
Kurtosis		12.779	.313	6.752	.313

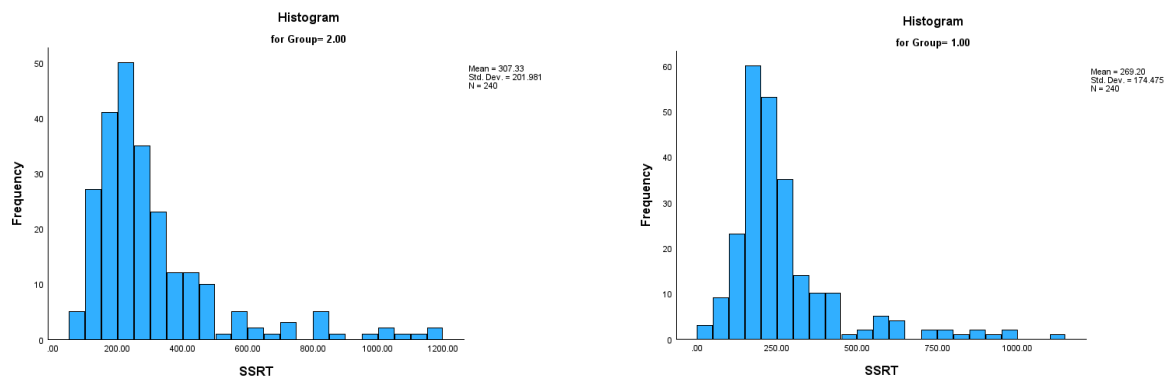
Note: OE = omission errors.

As with the WCST and GNG models, histograms were run in SPSS to also test the normality assumption and boxplots and scatter plots for linearity and univariate outliers for the SST model. Significant multivariate outliers were identified using Mahalanobis distance and

Cook's distance. Histograms were run on all three dependent (outcome) variables. Generally, all frequency distributions of the dependent (outcome) variables did not meet normality assumptions. Figure 41 visually shows the results of histogram for the test of the linearity assumption for the treatment group and the control group for SSRT. The distributions were uniformly positively skewed as confirmed by the descriptive statistics shown at Table 54. All skew values were greater than 1.5, where 2 is a common threshold used in the context of the normality assumption.

Figure 41

Histogram of SSRT Distribution for Treatment and Control Groups for the SST Model



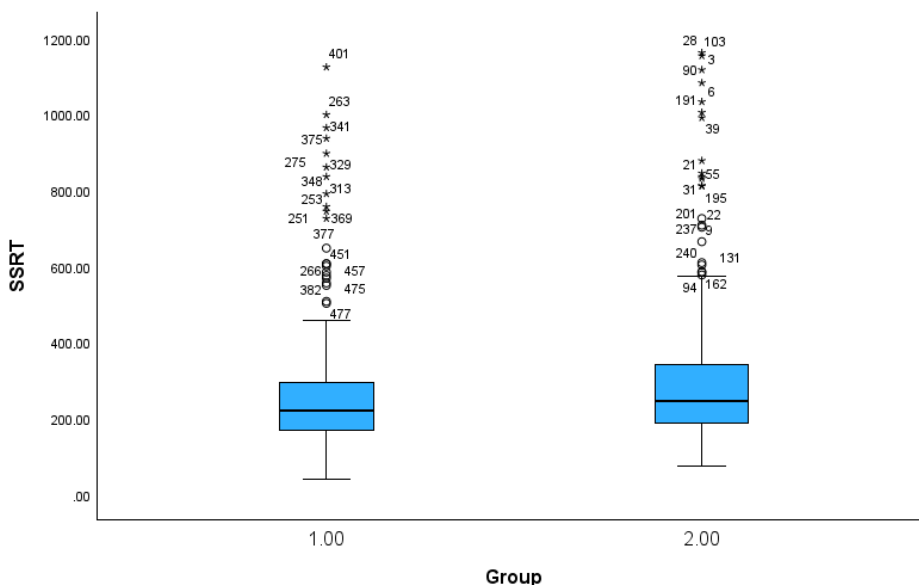
Note: SSRT = stop signal reaction time. Group 2 = treatment group (high Factor I motor impulsivity (FI-MI), Group 1 = control group (low FI-MI).

With respect to univariate outliers, Figure 42 shows Boxplots for both the treatment (high BIS-11 Factor I motor impulsivity [FI-MI]) and control (low FI-MI) groups for SSRT for the SST model. The box for the treatment group (high FI-MI, Group 2 in Figure 42) shows higher variability in the interquartile range (*IQR*; middle 50%) of SSRT values than the box for the control group (low FI-MI, Group 1 in Figure 42). The median line for the control group

(Group 1) shows a thicker box above the median line, confirming a positive skew for the *IQR* of SSRT values for the control group while the box thickness above and below the median line for the treatment group shows a more even distribution. Whiskers ($1.5 \times IQR$) also show greater variability for the treatment (high) group than the control (low) group. The control group had four positive outliers ($1.5 - 3 \times IQR$), 16 extreme positive outliers ($>3 \times IQR$), and no negative outliers. The treatment group had four positive outliers, 11 extreme positive outliers, and two negative outliers. The outliers of the control (low) control group comprised 1.7% of cases (participants) and the extreme outliers comprised 6.7%. The outliers of the treatment (high) group comprised 2.5% of cases and the extreme outliers comprised 4.6%. Both groups have total outliers higher than the maximum of 5% expected for a normal distribution.

Figure 42

Boxplots of SSRT for Treatment and Control Groups for the SST Model

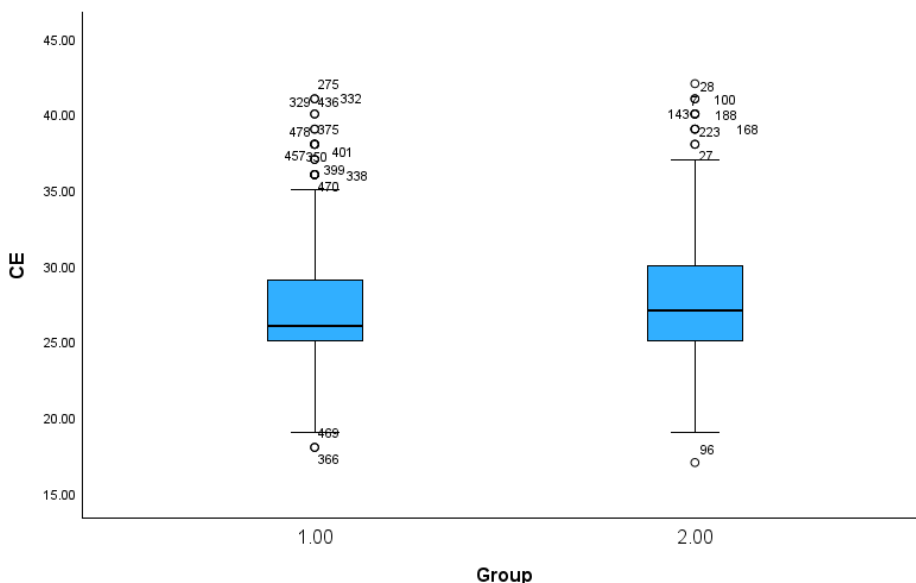


Note: SSRT = stop signal reaction time. Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high Factor I motor impulsivity (FI-MI) treatment group.

Figure 43 shows Boxplots for both the treatment (high BIS-11 Factor I motor impulsivity) and control (low FI-MI) groups for CE for the SST model. The box for the control group (low FI-MI, Group 1 in Figure 43) has slightly less variability but much higher positive skew in the interquartile range (*IQR*; middle 50%) of CE values for the SST than the treatment group (high FI-MI, Group 2 in Figure 43). Whiskers ($1.5 \times IQR$) also show greater variability and positive skew for the treatment (high) group than the control (low) group. The control group had seven positive outliers ($1.5 - 3 \times IQR$) and two negative outliers and no extreme outliers. The treatment group had six positive outliers and one negative outlier and no extreme outliers. The outliers of the control (low) control group comprised 3.8% of cases (participants). The outliers of the treatment (high) control group comprised 2.9% of cases.

Figure 43

Boxplots of CE for Treatment and Control Groups for the SST Model

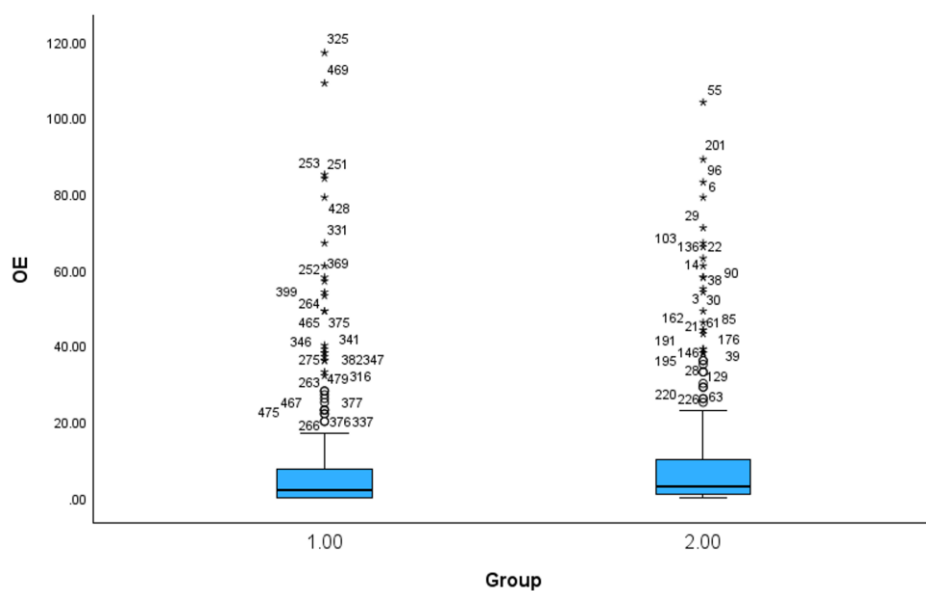


Note: CE = commission errors. Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high Factor I motor impulsivity (FI-MI) treatment group.

Figure 44 shows Boxplots for both the treatment (high BIS-11 Factor I motor impulsivity) and control (low) groups for OE for the SST model. The boxes for the treatment (high FI-MI, Group 2 in Figure 44) and the control (low FI-MI, Group 1 in Figure 44) group both show low variability in the interquartile range (*IQR*; middle 50%). The median line in the Boxplot also suggests a significantly positively skewed *IQR* for both groups with zero effect, most participants had very few or no omission errors. Whiskers ($1.5 \times IQR$) show somewhat greater variability for the treatment (high) group than for the control (low) group. The control group had eight positive outliers ($1.5 - 3 \times IQR$) and 19 extreme positive outliers ($>3 \times IQR$). The treatment group had five positive outliers and 17 extreme positive outliers. The outliers of the control (low) control group comprised 3.3% of cases (participants) and the extreme outliers comprised 7.9%. The outliers of the treatment (high) control group comprised 2.1% of cases and the extreme outliers comprised 7.1%. In both groups there are significantly more outliers than expected for a normal distribution. Overall, the Box plots suggest that OE represents loss of focus or disengagement from the task with the treatment (high FI-MI) group having slightly higher loss of attention and such attentional lapses contribute to trait motor impulsivity.

Figure 44

Boxplots of OE for Treatment and Control Groups for the SST Model

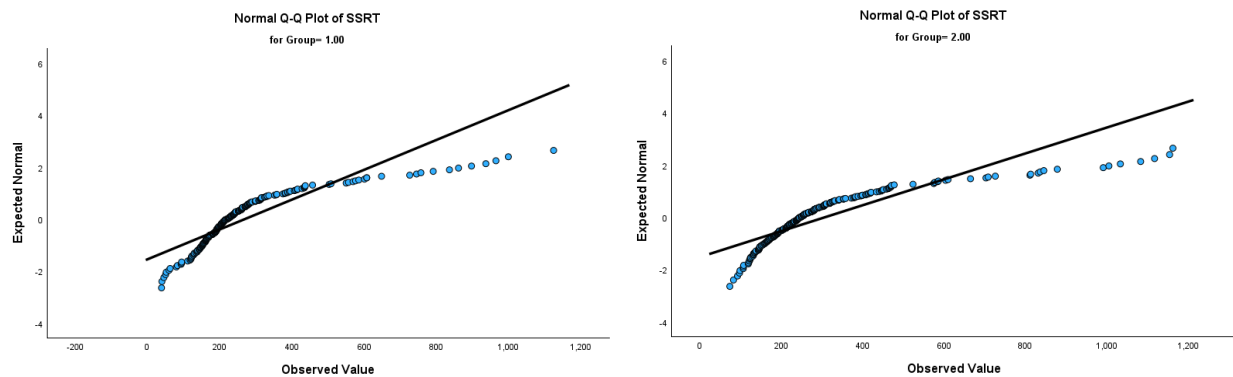


Note: OE = omission errors. Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high Factor I motor impulsivity (FI-MI) treatment group.

Figure 45 shows Q-Q Plots (Quantile-Quantile Plots) for SSRT for both Group 1 (the control, low BIS-11 FI motor impulsivity group) and Group 2 (the treatment, high FI-MI group). The diagonal line represents a putative normal distribution. Both groups show a leptokurtic distribution, demonstrating heavy fat tailed rightly skewed SSRT data generally consistent with the Box plots.

Figure 45

Q-Q Plots of Treatment and Control Groups for SSRT for the SST Model

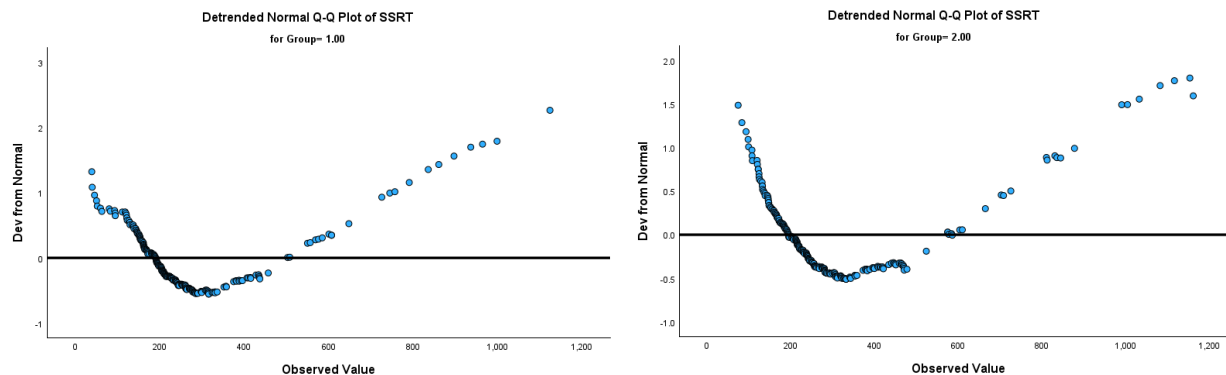


Note: SSRT = stop signal reaction time, Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high FI-MI treatment group.

Figure 46 shows a detrended normal Q-Q plot of SSRT for the SST model, which shows the residuals (quantile delimited on y-axis) between observed and expected normal SSRT values (millisecond values on x-axis) for each of the control (low FI-MI) and treatment (high FI-MI) groups. Both plots support deviations from normality from prior plots with excess values at the extremes and fewer central tendencies than expected in a normal distribution. This suggested bimodal tendency or subpopulations within groups, particularly the control group.

Figure 46

Detrended Normal Q-Q Plot of SSRT for the SST Model

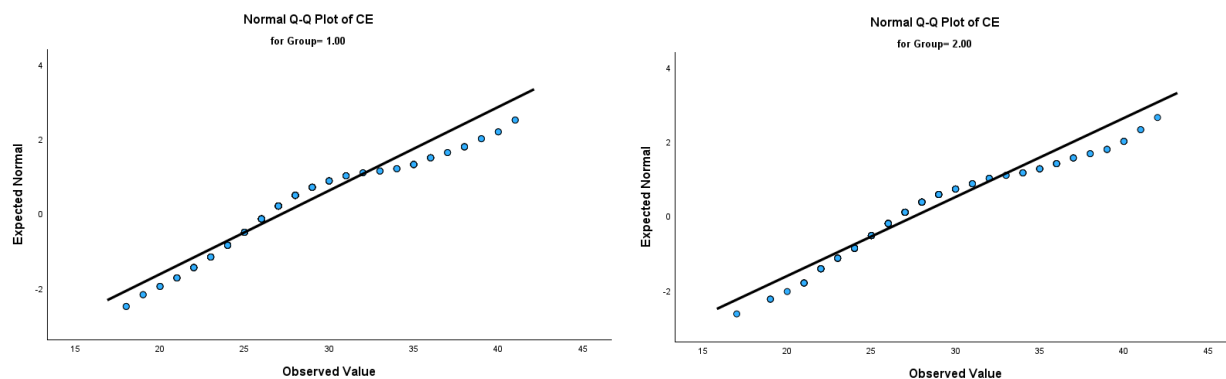


Note: SSRT = stop signal reaction time, Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high FI-MI treatment group.

Figure 47 shows Q-Q Plots (Quantile-Quantile Plots) for CE in the SST model for both Group 1 (the control, low BIS-11 FI motor impulsivity group) and Group 2 (the treatment, high FI-MI group). The diagonal line represents a putative normal distribution. Both groups also show a substantially normal distribution contrasting with the results for SSRT above.

Figure 47

Q-Q Plots of Treatment and Control Groups for CE for the SST Model

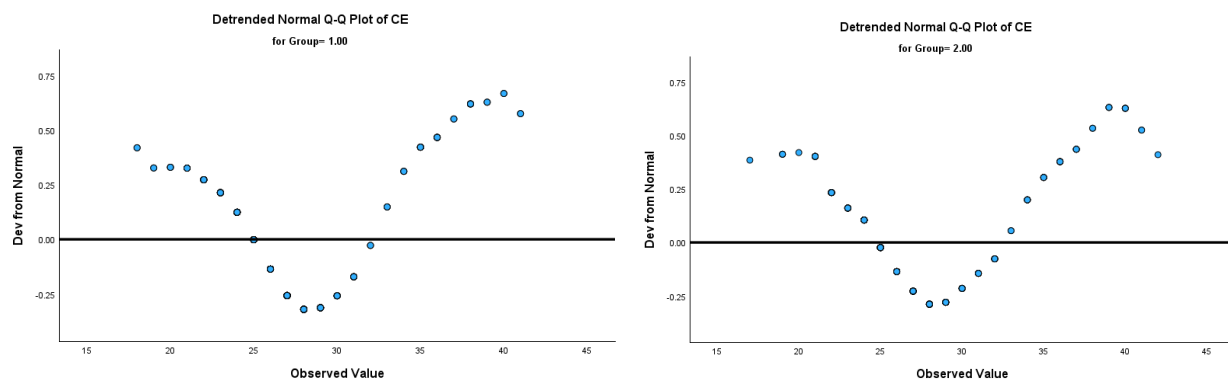


Note: CE = commission errors, Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 1 = high FI-MI treatment group.

Figure 48 shows a detrended (extracting any reference to mean and variance) normal Q-Q plot of CE for the SST model which shows the residuals (quantile delimited on y-axis) between observed and expected normal CE values (millisecond values on x-axis) for each of the control (low FI-MI) and treatment (high FI-MI) groups. Both plots confirm normality described above for CE.

Figure 48

Detrended Normal Q-Q Plot of CE for the SST Model



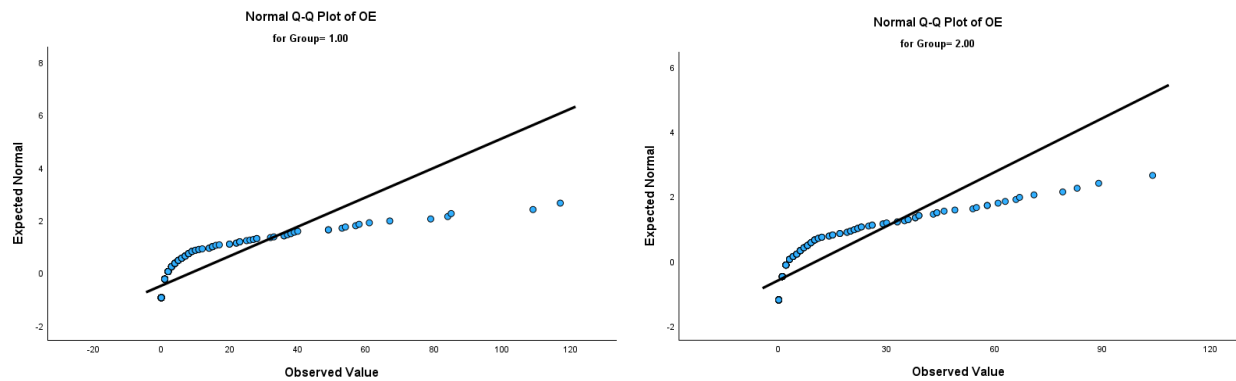
Note: CE = commission errors. Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 1 = high FI-MI treatment group.

Figure 49 shows Q-Q Plots (Quantile-Quantile Plots) for OE for the SST model for both Group 1 (the control, low BIS-11 FI motor impulsivity group) and Group 2 (the treatment, high FI-MI group). Both groups also show a leptokurtic distribution demonstrating moderately

positively tailed OE data deviating from normality at the higher levels and remarkably more so for the control group than for the treatment group.

Figure 49

Q-Q Plots of Treatment and Control Groups for OE for the SST Model

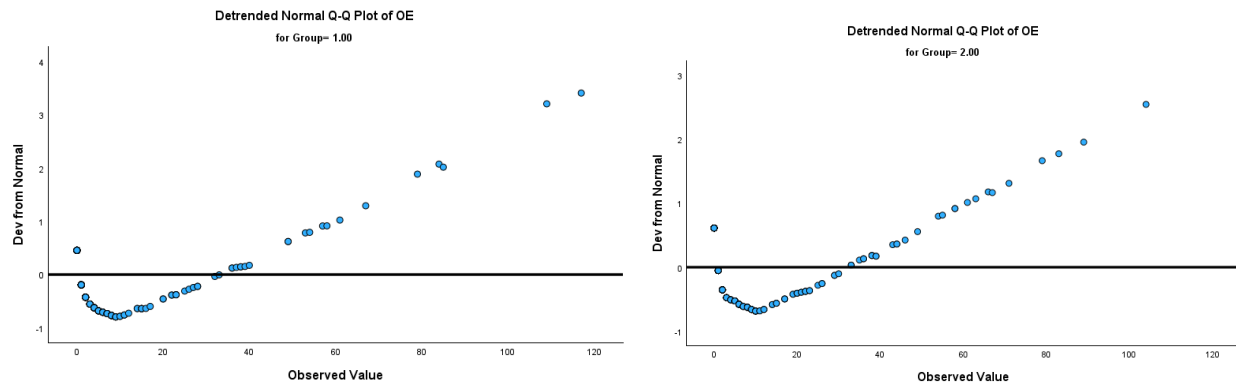


Note: OE = omission errors, Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high FI-MI treatment group.

Figure 50 shows a detrended normal Q-Q plot of OE for the SST model which shows the residuals (quantile delimited on y-axis) between observed and expected normal OE values (millisecond values on x-axis) for each of the control (low FI-MI) and treatment (high FI-MI) groups. Both plots demonstrate leptokurtic positively skewed tailed non-normal distributions.

Figure 50

Detrended Normal Q-Q Plot of OE for the SST Model

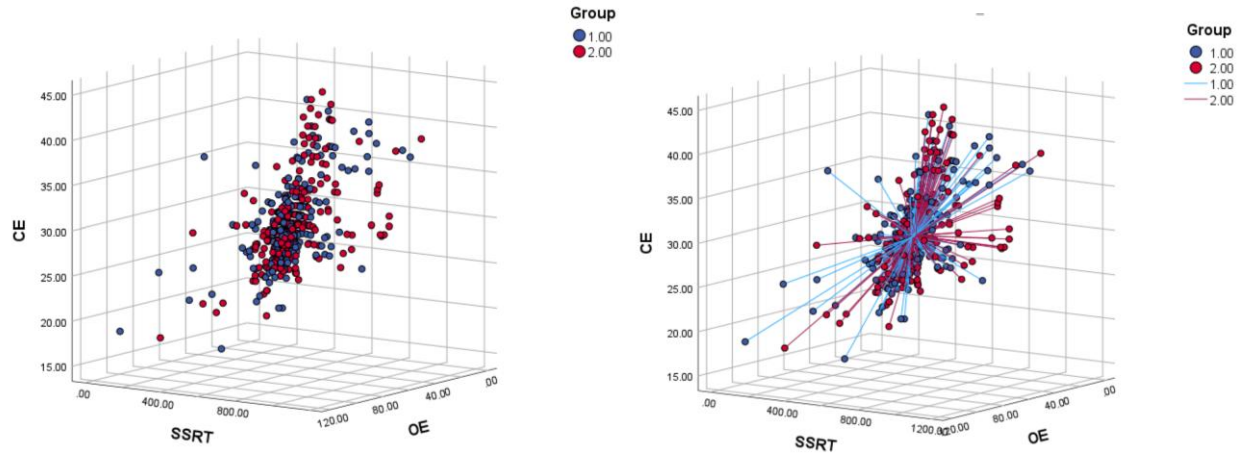


Note. OE = omission errors. Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high FI-MI treatment group.

Figure 51 displays three-dimensional scatter plots of SSRT, CE, and OE by categorical group membership (low Factor I motor impulsivity, Group 1; high Factor I motor impulsivity, Group 2), with and without centroids. Both groups exhibit triangular or comet-tail distribution patterns characterized by dense clustering at lower values with gradual dispersion toward higher values across all three dimensions. Substantial overlap between groups is evident in the three-dimensional space. Counterintuitively, Group 1 demonstrates greater multivariate dispersion than Group 2, with the Group 1 centroid positioned at higher values across multiple dimensions. The visual patterns indicate potential group differences requiring statistical verification through MANOVA analysis.

Figure 51

Three Dimensional Scatter Plot Matrix/Centroid by H-FIMI and L-FIMI for The SST Model

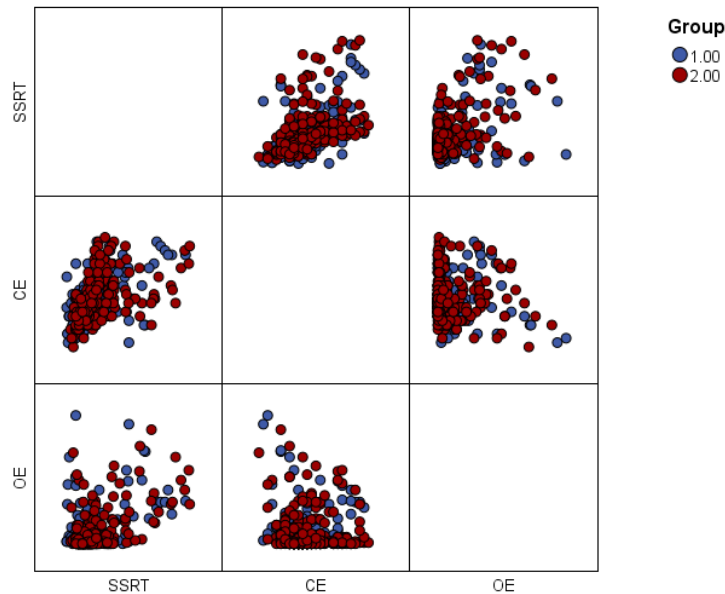


Note: SSRT = stop signal reaction time, CE = commission errors, OE = omission errors, Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high FI-MI treatment group.

Figure 52 presents a scatterplot matrix illustrating pairwise relationships among the three dependent variables (SSRT, CE, and OE). SSRT and CE demonstrate a strong positive linear relationship (r appears $> .70$), with Group 1 (low FI-MI) showing greater dispersion than Group 2 (high FI-MI). SSRT and OE exhibit a moderate positive correlation with more pronounced outliers in Group 1. The relationship between CE and OE appears weaker, suggesting these measures capture distinct aspects of inhibitory control performance. The differential group dispersions across variable pairs indicate potential heterogeneity of covariance matrices, warranting evaluation of MANOVA assumptions.

Figure 52

Scatterplot Matrix of SSRT, CE, and OE for the SST Model



Note: SSRT = stop signal reaction time, CE = commission errors, OE = omission errors. Group 1 = low Factor I motor impulsivity (FI-MI) control group, Group 2 = high FI-MI treatment group.

Results For Hypothesis 3, RQ 3, SST Model

A one-way (one-factor) between-subjects unpaired multivariate analysis of variance (MANOVA) was conducted to examine the effect of the dichotomous (categorical) independent predictor variable groupings (factor levels) of top and bottom quartile Factor I (FI) motor impulsivity (FI-MI) scores on the BIS-11 on three dependent (outcome) variables of stop signal reaction time (SSRT, in milliseconds), commission errors (CE), and omission errors (OE) of the stop signal laboratory behavioral task (SST) measure. Analysis of the MANOVA results in SPSS-30 revealed no statistically significant effect of BIS-11 FI motor impulsivity (FI-MI) dichotomous independent (predictor) variable group (low FI-MI [control] vs. high FI-MI

[treatment]) on the linear combination (variate) of the dependent (outcome) variables of SSRT, CE, and OE, $F(3, 476) = 1.662$, $p = .174$, partial $\eta^2 = .010$. Univariate tests, however, did reveal a practically significant shadow effect for SSRT, $F(1,478) = 4.900$, $p = .027$, partial $\eta^2 = .010$, with small effect indicating that the high BIS-11 FI-MI treatment group demonstrated practically poorer inhibitory control than the low BIS-11 FI-MI control group in terms of stopping time as measured by the SSRT. No significant effects were found for CE, $F(1,478) = 0.681$, $p = .409$, partial $\eta^2 = .001$, or OE, $F(1,478) = 1.373$, $p = .242$, partial $\eta^2 = .003$. Post hoc tests were not conducted since the null hypothesis for Hypothesis 3 (RQ3) could not be rejected and MANOVA univariate tests already tested any pairwise comparisons and between subjects effects and there are only two groups of the independent variable. Details of the multivariate and univariate tests are discussed below.

Multivariate Tests: MANOVA for the SST Model

Table 55 presents the multivariate test results for the SST model (Hypothesis 3). Due to violation of the homogeneity of covariances assumption, Pillai's trace was selected as the primary test statistic, as it is more robust to assumption violations and less sensitive to violations of MANOVA assumptions than alternative multivariate tests.

Pillai's trace, $V = .010$, $F(3, 476) = 1.662$, $p = .174$, indicated that the differences between the control group (low BIS-11 Factor I motor impulsivity) and treatment group (high Factor I motor impulsivity) were not statistically significant. The effect size was very small, partial $\eta^2 = .010$, indicating that only 1% of the variance in the linear combination (linear variate) of SSRT, CE, and OE was explained by group membership.

As discussed in Chapter 3, since there is only one linear variate (and one eigenvector and eigenvalue) due to the model containing only one independent predictor variable with two levels,

Effect	Value	Hypoth.				Partial	Noncent.	Observed
		F	df	Error df	p	η^2	Parameter	Power ^c
Pillai's V	0.010	1.662 ^b	3.000	476.000	.174	.010	4.986	.436
Wilks' Λ	0.990	1.662 ^b	3.000	476.000	.174	.010	4.986	.436
Hotelling's T^2	0.010	1.662 ^b	3.000	476.000	.174	.010	4.986	.436
Roy's θ	.0010	1.662 ^b	3.000	476.000	.174	.010	4.986	.436

^a Design: Intercept + Group. ^b Exact statistic. ^c Computed using $\alpha = .05$.

Univariate Tests Used to Build the MANOVA Model for the SST

Table 58 shows the results of Levene's Test for Equality of Variances for each of the dependent (outcome) variables of SSRT, CE, and OE. Using mean as the basis, because all the p values are greater than .05 the null hypothesis of equal variances cannot be rejected so the assumption of homogeneity of variance (homoscedasticity) is met for SSRT, $F(1, 478) = 3.069$, $p = .080$, CE, $F(1,478) = 1.042$, $p = .308$, and OE, $F(1,478) = 1.124$, $p = .290$. Only SSRT was close to significance, consistent with graphical comparisons above. Note that median and trimmed mean results provide robust support for the above findings because those significance levels are also greater than .05.

Table 58*Levene's Test of Equality of Error Variances^a for the SST Model*

	Levene's <i>F</i>	<i>df1</i>	<i>df2</i>	<i>p</i>
SSRT				
Based on Mean	3.069	1	478	.080
Based on Median	1.914	1	478	.167
Based on Median and with adjusted <i>df</i>	1.914	1	469.146	.167
Based on trimmed mean	2.411	1	478	.121
CE				
Based on Mean	1.042	1	478	.308
Based on Median	0.749	1	478	.387
Based on Median and with adjusted <i>df</i>	0.749	1	477.512	.387
Based on trimmed mean	1.103	1	478	.294
OE				
Based on Mean	1.124	1	478	.290
Based on Median	0.988	1	478	.321
Based on Median and with adjusted <i>df</i>	0.988	1	477.823	.321
Based on trimmed mean	1.349	1	478	.246

Note: Tests the null hypothesis that the error variance of the dependent variable is equal across groups. SSRT = stop signal reaction time, CE = commission errors, OE = omission errors.

^a Design: Intercept + Group.

Table 59 shows the results of tests of between-subject effects via the univariate F s (separate univariate ANOVAs) for each dependent (outcome) variable of SSRT, CE, and OE. This test informs determination of statistically significant differences between the two predictor groups (treatment, high MI, or control, low MI) on each individual dependent (outcome) variable. The results for the model sum of squares for the groups show no statistically significant differences between groups for CE, $F(1,478) = 0.681$, $p = .409$, partial $\eta^2 = .001$, and OE, $F(1,478) = 1.373$, $p = .242$, partial $\eta^2 = .003$, and a statistically significant difference between groups for SSRT with small effect, $F(1,478) = 4.900$, $p = .027$, partial $\eta^2 = .010$. This suggested that, to the extent that there were group differences, SSRT was the primary contributor to those differences. As noted previously, the treatment group (high FI-MI, Group 2) had a 38.1 ms longer mean SSRT, $\bar{x} = 307.3$ ms, $SD = 202.0$, than the control group (low FI-MI, Group 1), $\bar{x} = 269.2$ ms, $SD = 174.5$, along with greater variability. As SSRT is an indicator of behavioral response inhibition (BRI), the high BIS-11 FI-MI treatment group demonstrates practically poorer inhibitory control than the low BIS-11 FI-MI control group. This observation represents a shadow effect of the univariate SSRT focused SST model respecting failure to disprove the null hypothesis of the MANOVA model. The corrected model shows the total sums of squares, which demonstrates how much variance is explained by all predictors (independent variable factor levels) in the SST model. Values for the corrected models were identical to the group model because there were no covariates in the model, so the corrected model was simply the effect of group plus the intercept.

Source DV	Type III SS	df	Mean Square	F	Sig.	partial	Noncent.	Observed
						η^2	Parameter	Power ^d
SSRT	57086246.330	480						
CE	371927.000	480						
OE	200147.000	480						
Corrected Total								
SSRT	17200344.297	479						
CE	10081.081	479						
OE	154536.498	479						

Note: SSRT = stop signal reaction time, CE = commission errors, OE = omission errors.

^a $R^2 = .010$ (Adjusted $R^2 = -.008$), ^b $R^2 = .001$ (Adjusted $R^2 = .001$), ^c $R^2 = .003$ (Adjusted $R^2 = .001$), ^d Computed using $\alpha = .05$.

Table 60 shows parameter estimates for SST (Hypothesis 3) for each dependent (outcome) variable of SSRT, CE, and OE. In this study, parameter estimates were not necessary because there were no covariates, although parameter estimates can be useful for determining the magnitude and direction of effects of the independent (predictor) variable on the dependent variables as well as test, confirm, or support interpretation of main effects, Levene's test, and tests of between-subject effects via univariate F s (Field, 2024; George & Mallery, 2024). There was a statistically significant result for SSRT, $B = -38.136$, $p = .027$, and partial $\eta^2 = 0.010$, with no statistically significant result for CE, $B = -.346.409$, $p = .409$, partial $\eta^2 = 0.001$, or OE, $B = -1.921$, $p = .242$, partial $\eta^2 = .003$, which was consistent with the other tests. Note that the B statistic is negative because SPSS-30 sets the first numerical category (the low FI-MI control

group in this case) as the reference group and, as such, the statistics are relative to the other group (the high FI-MI treatment group), which is set at zero. Overall, the observed power of SSRT of .598 indicated moderate power to detect a small, but potentially meaningful effect consistent with the literature that poorer trait motor impulsivity corresponds with poorer inhibitory control (prepotent response extinction) in the SST.

Table 60

Parameter Estimates for SST Model

		95% Confidence								
			Std.			Interval		partial	Noncent.	Obsvd.
DV	Parameter	<i>B</i>	Error	<i>t</i>	<i>p</i>	Lower	Upper	η ²	Param	Power ^b
SSRT										
	Intercept	307.331	12.182	25.227	<.001	283.393	331.269	.571	25.227	1.000
	[Group=1.00]	-38.136	17.229	-2.214	.027	-71.989	-4.283	.010	2.214	.598
	[Group=2.00]	0 ^a	.	.	.	.	.	.	.	.
CE										
	Intercept	27.629	.296	93.270	<.001	27.047	28.211	.948	93.270	1.000
	[Group=1.00]	-.346	.419	-.826	.409	-1.169	0.477	.001	0.826	.131
	[Group=2.00]	0 ^a	.	.	.	.	.	.	.	.
OE										
	Intercept	10.708	1.159	9.240	<.001	8.431	12.986	.152	9.240	1.000
	[Group=1.00]	-1.921	1.639	-1.172	.242	-5.141	1.300	.003	1.172	.216
	[Group=2.00]	0 ^a	.	.	.	.	.	.	.	.

Note: SSRT = stop signal reaction time, CE = commission errors, OE = omission errors.

^a This parameter is set to zero because it is redundant. ^b Computed using $\alpha = .05$.

Table 61 shows the between-subjects sum of squares cross product (SSCP) matrices of the SST model. The SSCP matrices are foundational precursors to calculation of eigenvalues for the F statistic and used to explore the pattern of the data via cross-products (uncentered covariance matrix) to characterize the relationship (covariability) between the dependent (outcome) variables of SSRT, CE, and OE. As noted in Chapter 3's discussion of MANOVA mathematics, the SSCP is calculated in MANOVA, after extracting the eigenvalue from the eigenvector for each dependent (outcome) variable, via least squares regression to calculate the sum of squares. Then, MANOVA calculates the sum of squares of the error (within groups unsystematic residual variance) and then total sum of squares. Next, MANOVA calculates the sum of the cross-product covariance (via matrix and linear algebra) and finally the SSCP matrices. SSCP matrices thus enable MANOVA to consider cross correlations between the dependent (outcome) variables, which ANOVAs cannot do.

The hypothesis intercept matrix in Table 61 provides the total variability of the model resulting primarily from the intercept. The group matrix below provides the sum of squares and cross product (SSCP) output to characterize the effect of the independent (predictor) variable of FI-MI (high and low groups) on group differences of the dependent (outcome) variables. The error matrix below that on Table 61 provides the residual variance in light of group differences. The group diagonals represent the sum of squares (SS) and the off-diagonals represent the cross-products (CP). Thus, the diagonals ($SSRT = 174524.828$, $CE = 14.352$, $OE = 442.752$) show the magnitude of how much variance each dependent (outcome) variable contributes to the group difference. The hypothesis sum of squares for SSRT (174524.828) is much larger than that for

CE and OE, supporting the previous observations regarding the effect of SSRT dependent (outcome) variable. Positive off-diagonals indicate a positive relationship (correlation).

The within group error matrix represents unexplained variability in the model. The diagonal for SSRT, CE, and OE contain values indicating a very high variance (determinants) in SSRT, but lower values by orders of magnitude for OE, and for CE in that order. Off-diagonal negative cross product values in the error matrix (-742.508) for CE and OE suggest negative correlation between the two. Because the error variance is significantly higher than the group variance (98 times larger for SSRT, 701 times larger for CE, 348 times larger for OE), the SSCP matrices support the previous indicators that, notwithstanding SSRT having practical, but not statistical significance, BIS-11 FI-MI predicts a very small fraction of the total variance in performance in the SST laboratory behavioral measure.

Table 61

Between-Subjects SSCP Matrix for the SST Model

		SSRT	CE	OE
Hypothesis	Intercept			
	SSRT	39885902.033	3799019.724	1348783.162
	CE	3799019.724	361845.919	128467.794
	OE	1348783.162	128467.794	45610.502
	Group			
	SSRT	174524.828	1582.654	8790.406
	CE	1582.654	14.352	79.715
	OE	8790.406	79.715	442.752

	SSRT	CE	OE
Error			
SSRT	17025819.470	207452.621	784040.132
CE	207452.621	10066.729	-742.508
OE	784040.132	-742.508	154093.746

Note: Based on Type III Sum of Squares. SSRT = stop signal reaction time, CE = commission errors, OE = omission errors.

Table 62 shows the residual SSCP matrices for the SST model. It contains the variance-covariance (mean sum of squares-mean cross product) matrix (mean form of the SSCP matrix) and the correlation matrix. As described in Chapter 3, this measure interrogates any error (unexplained variance [discriminant]) and covariances after fitting the model (SST model in this case).

Starting with the correlation matrix, the diagonals of unity represent perfect self-variable correlation and off-diagonals characterize the direction and strength of relationships among the three dependent (outcome) variables of SSRT, CE, and OE. Standardizing the covariance matrix here yields Pearson correlation coefficients (r). The results indicate a moderate to strong positive correlation, $r = .501$, between SSRT and CE, a moderate correlation, $r = .484$, between SSRT and OE, and virtually no correlation, $r = -.019$, between CE and OE, which is consistent with prior observations. These results suggest that CE is more sensitive than OE to SSRT with longer reaction times decreasing commission errors. The diagonal of the residual SSCP matrix array contains high values (mRT = 4,469,675.952, CE = 31,954.901, OE = 247,132.37), suggesting significant residual variability. The shared covariance suggests moderate multicollinearity

concerns for MANOVA assumptions, but not significant enough to suggest variable redundancy. The negative off-diagonal values (-1.553) for the cross-products of CE and OE suggest that they covary. Overall, the correlational structure confirms the dominance of SSRT for multivariate effects.

Table 62

Residual SSCP Matrix for the SST Model

		SSRT	CE	OE
Sum-of-Squares and Cross-Products				
	SSRT	17025819.470	207452.621	784040.132
	CE	207452.621	10066.729	-742.508
	OE	784040.132	-742.508	154093.746
Covariance				
	SSRT	35618.869	434.001	1640.251
	CE	434.001	21.060	-1.553
	OE	1640.251	-1.553	322.372
Correlation				
	SSRT	1.000	.501	.484
	CE	.501	1.000	-.019
	OE	.484	-.019	1.000

Note: SSRT = stop signal reaction time, CE = commission errors, OE = omission errors.

Table 63 shows the estimated marginal means describing the adjusted means for each dependent (outcome) variable of SSRT, CE, and OE by dichotomous group (BIS-11 F1 low FI-MI [group 1], and high FI-MI [group 2]). The treatment group (high FI-MI) had higher SSRT, $\bar{x} = 307.3$ ms, [283.4, 331.3], $SE = 12.182$, than the control group (low FI-MI) $\bar{x} = 269.2$ ms, [245.3, 293.1], $SE = 12.182$. The confidence intervals overlap by about 10ms, but do not pass zero and still represent some practical significance, $p = .027$. The difference between the treatment group (high FI-MI), $\bar{x} = 27.6$ [27.0, 28.2], $SE = .296$, and control (low FI-MI), $\bar{x} = 27.3$ [26.7, 27.9], $SE = .296$, group was insignificant, with heavily overlapping confidence intervals. Similarly, the difference between the treatment group (high FI-MI), $\bar{x} = 10.7$ [8.4, 13.0], $SE = 1.159$, and control (low FI-MI), $\bar{x} = 8.8$ [6.5, 11.1], $SE = 1.159$, group was insignificant. Overall, the triangulation between descriptive statistics, parameter estimates, and marginal means confirm the previous results of some significance of SSRT driving differences between BIS-11 high FI-MI and low FI-MI treatment and control groups, but not significant enough for the MANOVA model (at least before removal of influential outliers as described later in Chapter 4).

Consequently, post-hoc testing is not required for the SST model as the above sufficiently confirm a shadow significant effect of SSRT ($p = .027$) as a predictor of differences prepotent response extinction of BRI between high trait BIS-11 Factor I motor impulsivity (FI-MI) and low FI-MI, but no significance in a linear combination of the three dependent (outcome) variables of SSRT, CE, and OE for the SST model.

Table 63*Estimated Marginal Means for the SST Model*

DV	Group	$\bar{x}$	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
SSRT	Control (L-FIMI)	269.195	12.182	245.257	293.133
	Treatment (H-FIMI)	307.331	12.182	283.393	331.269
CE	Control (L-FIMI)	27.283	0.296	26.701	27.865
	Treatment (H-FIMI)	27.629	0.296	27.047	28.211
OE	Control (L-FIMI)	8.788	1.159	6.510	11.065
	Treatment (H-FIMI)	10.708	1.159	8.431	12.986

Note: SSRT = Stop Signal Reaction Time; CE = Commission Errors; OE = Omission Errors.

Group 1 = Low FI-MI (Control); Group 2 = High FI-MI (Treatment).

Evaluation of the Findings, Theoretical Framework Validation

The above empirical findings from the three models (BIS-11 + WCST, GNG, SST laboratory behavioral measures) provided a foundation for evaluating this study's theoretical postulates incorporated into the three main and six sub-hypothesis and their alignment with existing literature. Note that due to the complexity and interconnected nature of the multivariate analyses, evaluation of findings has been integrated throughout the results sections to maintain contextual flow and theoretical coherence. This section provides a consolidated theoretical framework validation drawing from those distributed evaluations. Due to the complexity of this study and its analytical framework, this evaluation examines, in an integrated fashion, how the results from Research Questions 1-3 collectively address the stated problem of inadequate

endophenotype characterization (discrimination and decomposition) and support the integrated RDoC-Barkley theoretical framework.

The following analysis connects the statistical findings to their theoretical implications, setting the foundation for the practical applications and recommendations discussed in Chapter 5. These findings arguably provide compelling validation of the integrated theoretical framework combining RDoC latent variable endophenotype decomposition with Barkley's theory of inhibitory deficits. The successful discrimination of high versus low Factor I motor impulsivity BIS-11 groups across distinct laboratory behavioral measures (models) confirms the viability of the deep endophenotyping approach, with each significant finding directly mapping onto predicted theoretical constructs.

Research Question 1: WCST Model Validation: NPE Deep Decomposed Endophenotype

Non-perseverative errors (NPE) from the WCST emerged as a robust indicator of cognitive flexibility deficits, $p = .011$, Cohen's $d = -0.234$, supporting Barkley's framework that behavioral response inhibition (BRI) underpins executive function performance. The Cook's distance leverage-residual sensitivity analysis discussed below confirmed the exceptional robustness of this finding, $p = .016$, demonstrating that NPE represents a stable decomposed endophenotype resistant to influential outlier effects. The WCST model's significant multivariate effects, $p = .041$, partial $\eta^2 = .017$, were driven specifically by NPE, confirming its validity as a decomposed endophenotype for cognitive flexibility deficits.

Research Question 2: GNG Model Validation: CE Deep Decomposed Endophenotype

Commission errors (CE) from the GNG task discriminated groups with high significance, $p = .001$, Cohen's $d = -0.297$, confirming prepotent response inhibition as a core facet of trait motor impulsivity. The Cook's distance sensitivity analysis discussed below not only confirmed

CE's robustness, $p = .007$, but also revealed omission errors (OE) as an additional significant predictor, $p = .012$, Cohen's $d = -0.250$, suggesting dual pathways of inhibitory control deficits. The robust multivariate effects, $p = .005$, partial $\eta^2 = .026$, establish CE as a reliable decomposed endophenotype for inhibitory control deficits.

Research Question 3: SST Model Validation: Mixed Effects-Sensitivity Analysis Discovery

The SST model initially showed non-significant multivariate effects, $p = .174$, though SSRT demonstrated a meaningful shadow effect, $p = .027$, partial $\eta^2 = .010$. However, the Cook's distance leverage-residual sensitivity analysis discussed below revealed substantial signal recovery, transforming the multivariate effect to significance, $p = .019$, and uncovering omission errors (OE) as a significant predictor, $p = .006$, Cohen's $d = -0.271$. This finding, combined with the parallel OE effect in the GNG model, $p = .012$, Cohen's $d = -0.250$, appears to suggest that sustained attention deficits represent a transdiagnostic feature of behavioral response inhibition (BRI) deficits across multiple RDoC paradigm laboratory behavioral measure contexts.

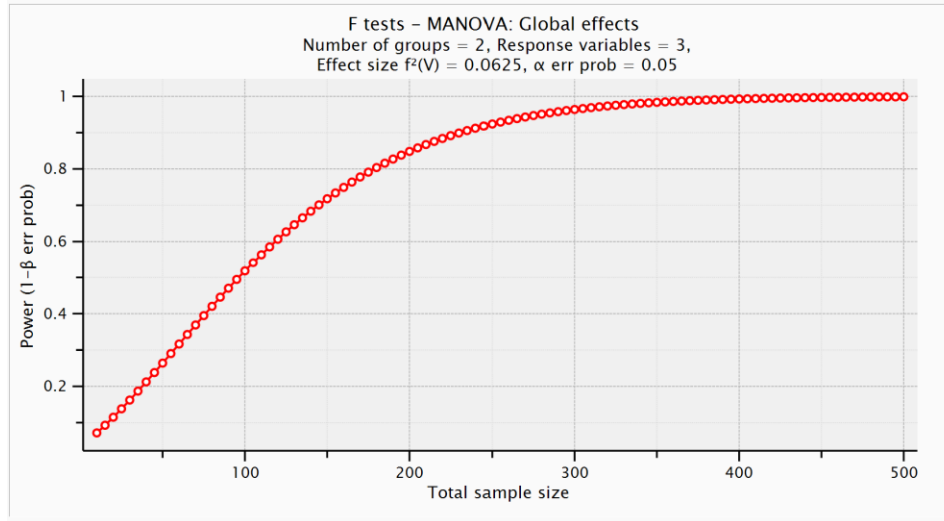
Integrated Theoretical Implications

These findings address the fundamental problem identified in Chapters 1 and 2—that the endophenotype literature has failed to adequately characterize and segregate the dimensionality of impulsivity constructs. The successful decomposition of behavioral response inhibition (BRI) into distinct, measurable facets (decomposed endophenotypes and features) that differentially associate with trait motor impulsivity provides empirical support for the RDoC premise that psychological constructs are best understood through their component dimensions rather than as unitary phenomena.

Implementation of Cook's Leverage-Residual Sensitivity Analysis

Following the outlier detection methodology and influence analysis established in Chapter 3, first, Mahalanobis Distance (using eigenvalues) was calculated globally for all nine dependent outcome variables for all three models and then individually for each model (i.e., WCST, GNG, SST). Next, Cook's leverage-residual (influence) sensitivity analysis was implemented to assess model robustness and examine potential improvements in effect size and statistical significance. The rationale for this sensitivity analysis was threefold: (a) to confirm that the primary findings are robust to the presence of influential outliers, (b) to potentially improve statistical power and effect size estimates by reducing error variance associated with extreme values, and (c) to provide a more stringent test of the hypotheses by working with the most reliable and representative data.

Given that the initial sample size ($n = 480$) substantially exceeded the minimum required for adequate power ($n = 280$), the removal of outlying cases (participants) was not expected to compromise statistical power, with actual power for the completed study of .998 (Figure 9) while potentially revealing effects that may have been obscured by influential cases. Figure 53 shows a G*Power analysis showing the relationship between sample size and statistical power for detecting medium effects, $f^2 = 0.063$, in a MANOVA model with a dichotomous two group independent predictor variable and three dependent outcome variables. Horizontal reference lines indicate that conventional adequate power (.80) would be achieved at approximately $n = 180$, and near-maximum power (≈ 1.00) would be achieved above $n = 400$. Study sample sizes of 480 (original) and 411 (refined, see below) both provided excellent near perfect statistical power.

Figure 53*G*Power Curve for Sample Size*

The cross-model removal procedure was executed as set forth in Chapter 3 using a master SPSS dataset containing all nine dependent outcome variables from the WCST, GNG, and SST models, with Cook's distance calculations performed globally and then sequentially for each model using the established threshold of 0.0083 (see Chapter 3). Cases flagged for removal based on Cook's distance violations in *any* of the three models were systematically excluded (by creating a 'Remove_Case' flag in SPSS-30) from all subsequent analyses to preserve the integrity of cross-model comparisons and convergence assessment of significant dependent outcome variables. Following case removal, MANOVA analyses were re-conducted on each of the three refined models and results systematically compared to the original main analyses to provide direct assessment of model robustness and quantify the impact of influential outliers on effect size estimates and statistical significance.

Outlier Detection Results

Mahalanobis distance analysis identified 24 cases (5.0%) exceeding the global threshold, $\chi^2 = 27.88$, $df = 9$, $p < .001$, across all nine dependent variables. Model-specific Mahalanobis distance analysis, $\chi^2 = 16.27$, $df = 3$, $p < .001$, revealed 16 cases (3.3%) flagged in the GNG model, eight cases (1.7%) in the SST model, and six cases (1.3%) in the WCST model.

Cook's distance analysis using the 0.0083 threshold identified 42 cases (8.8%) with influential leverage in the global analysis. Model-specific Cook's distance calculations revealed 33 cases (6.9%) exceeding the threshold in the GNG model, 40 cases (8.3%) in the SST model, and 23 cases (4.8%) in the WCST model. A comprehensive summary of outlier detection results by method and model is presented in Table 64.

Table 64

Summary of Outlier Detection Results by Method and Model

Detection Method	Global Analysis	WCST Model	GNG Model	SST Model	Total Unique Cases
Mahalanobis Distance	24 (5.0%)	6 (1.3%)	16 (3.3%)	8 (1.7%)	30 (6.3%) ^a
Cook's Distance	42 (8.8%)	23 (4.8%)	33 (6.9%)	40 (8.3%)	96 (20.0%) ^a
Aggregate Removal	—	—	—	—	69 (14.4%)

Note. WCST = Wisconsin Card Sorting Test; GNG = Go/No-Go Task; SST = Stop Signal Task.

^a Theoretical maximum assuming no overlap between models.

The pattern of outlier detection revealed material differences between global and model-specific approaches, as shown in Table 65. For Mahalanobis distance, the global analysis (5.0% flagged) identified fewer cases than the combined model-specific analyses, which would total 30 cases (6.3%) if there were no overlap between models. Conversely, Cook's distance analysis showed the opposite pattern, with the global analysis identifying 42 cases (8.8%) compared to model-specific analyses that would total 96 cases (20.0%) without overlap. This divergent pattern suggests that Cook's distance was more sensitive to model-specific influential cases, while Mahalanobis distance was more effective at identifying cases that were multivariately extreme across the broader variable (feature) space. The substantial difference between the theoretical sum of model-specific flagged cases (126 total) and the actual aggregate removal count (69 cases) indicated considerable overlap in outlier detection across models, with many cases flagged by multiple detection methods and across multiple models. This convergence provided confidence in the robustness of the outlier identification process and supports the aggregate removal strategy employed.

Table 65
Sample Composition Before and After Case Removal

Group	Original Sample	Cases Removed	Final Sample	Removal Rate
Low FI-MI (Control)	240	30	210	12.5%
High FI-MI (Treatment)	240	39	201	16.3%
Total	480	69	411	14.4%

Note. FI-MI = Factor I motor impulsivity on the Barratt Impulsiveness Scale-11 (BIS-11).

Implementation of the aggregate removal strategy for influential outliers resulted in 69 unique cases (14.4% of the original sample) flagged for removal across all three models. As detailed in Table 65, case removal was distributed unevenly between groups, with 30 cases (12.5%) removed from the low Factor I motor impulsivity (FI-MI) control group ($n = 210$ remaining) and 39 cases (16.3%) removed from the high FI-MI treatment group ($n = 201$ remaining). The resulting group sizes of 210 for the control group (low FI-MI) and 201 for the treatment group (high FI-MI) represented a minimal difference that fell well within acceptable parameters for MANOVA robustness, as the technique is robust to moderate group size differences when both groups maintain adequate sample sizes (Tabachnick & Fidell, 2013). The refined total sample of $n = 411$ (85.6% of the original MANOVA study group sample) maintained substantial statistical power, exceeding by 47% the minimum sample size requirement of $n = 280$ determined through G*Power analysis in Chapter 3, while removing cases with disproportionate influence on model parameter estimates.

To evaluate the appropriateness of the aggregate removal strategy, outlier patterns across the three models (WCST, GNG, SST) were examined. Using SPSS 30 syntax programming language, code was written to interrogate all Cook's flag filters. As shown in Table 66, of the 69 cases removed (14.4% of the original sample), 24 cases (34.8%) were identified as influential outliers across multiple models, while 45 cases (65.2%) were outliers in only one model. The multi-model breakdown revealed three cases problematic across all three models, with notable overlap between attention-based tasks (GNG + SST: 18 cases, 26.1% of removed cases). Single-

model outliers were distributed relatively evenly: WCST only (17 cases), SST only (17 cases), and GNG only (11 cases).

Table 66

Cook's Distance Outlier Pattern Analysis Across Three Models

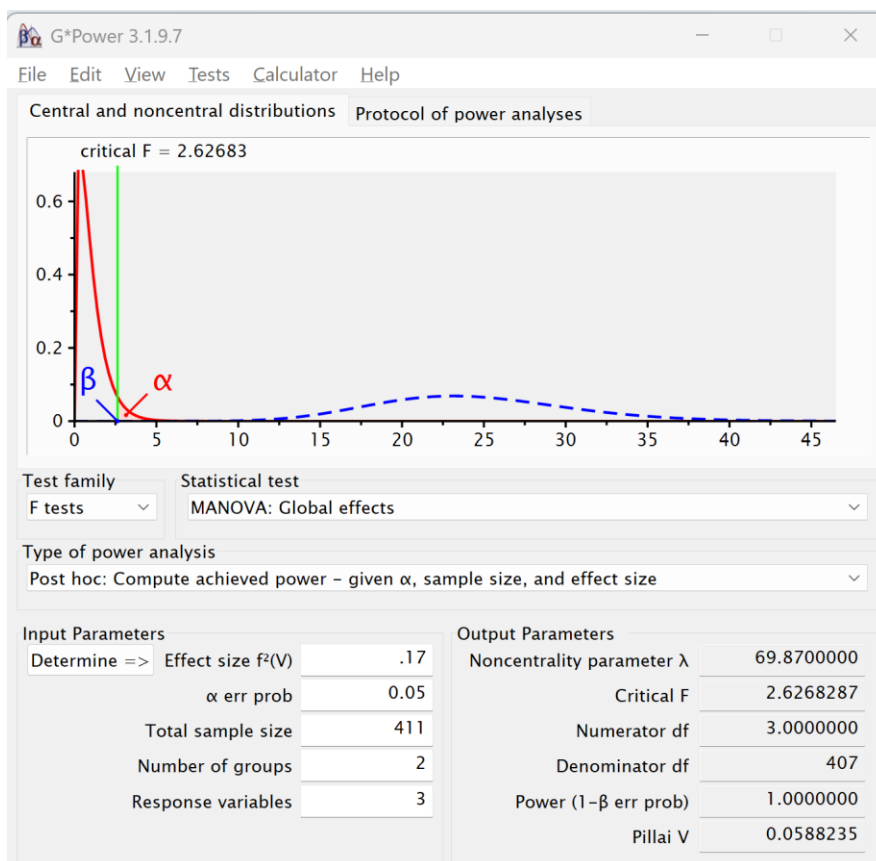
Outlier Pattern	# of Cases	% Removed Cases	% Total Sample
Multi-Model Outliers			
All three models (WCST + GNG + SST)	3	4.3%	0.6%
WCST + GNG only	1	1.4%	0.2%
WCST + SST only	2	2.9%	0.4%
GNG + SST only	18	26.1%	3.8%
Subtotal: Multi-Model	24	34.8%	5.0%
Single-Model Outliers			
WCST only	17	24.6%	3.5%
GNG only	11	15.9%	2.3%
SST only	17	24.6%	3.5%
Subtotal: Single-Model	45	65.2%	9.4%
Total Cases Removed	69	100.0%	14.4%
Cases Retained	411	—	85.6%

Note. WCST = Wisconsin Card Sorting Test, GNG = Go/No-Go Task, SST = Stop Signal Task. Outlier identification based on Cook's distance threshold of 0.0083.

The pattern analysis in Table 66 supported the aggregate removal approach, as the substantial multi-model overlap (34.8%) justified the conservative strategy of maintaining equivalent samples across all cognitive models for direct comparison, while the large remaining sample ($n = 411$) preserved adequate statistical power. Figure 54 shows that the achieved statistical power analysis for the refined study design ($n = 411$) following Cook's distance leverage-residual (influence) outlier removal demonstrated perfect power (1.00) for detecting observed effect sizes, $f^2 = .17$, in a MANOVA model with a dichotomous two group independent predictor variable and three dependent outcome variables. This confirmed more than adequate statistical power despite sample reduction from outlier removal.

Figure 54

Statistical Power Analysis for Cook's Refined sample.



MANOVA and Post Hoc Cook's Leverage-Residual Sensitivity Analysis Comparisons

After removal of influential cases in any one or more models from the entire data set, $n = 480 \rightarrow n = 411$, and creation of refined models for each laboratory behavioral task (WCST, GNG, SST), MANOVA and post hoc (when appropriate) analyses were re-conducted on each of the three refined models and the results were systematically compared to the original main analyses previously reported to provide direct assessment of model robustness and to quantify the impact of the cases that contained the removed influential outliers on effect size estimates and statistical significance.

Wisconsin Card Sorting Test (WCST) Model Results. The Cook's distance leverage-residual (influence) sensitivity analysis for the WCST model revealed moderate sensitivity in the multivariate effect, raising important interpretive considerations about the robustness of the overall prefrontal cortical dysfunction and cognitive flexibility findings and implications on BIS-11 Factor I trait motor impulsivity. As shown in Table 67, the multivariate test shifted from significance to marginal borderline non-significance after outlier removal, $F = 3.889, p = .009$, $\text{partial } \eta^2 = .024 \rightarrow F = 2.448, p = .063$, $\text{partial } \eta^2 = .018$, representing a meaningful change in statistical inference that warranted careful consideration.¹

¹ While this study appropriately took a conservative approach to statistical cutoffs and interpretation, it subscribed to warnings in the literature regarding overreliance of arbitrary p -value cut-offs, particularly when observed p -values are just above such cutoffs, creating artificial dichotomous binary classifiers that discard potentially meaningful results, undermining statistical analysis by converting probability to certainty (Greenland et al., 2016; Parry, 2021; Wasserstein & Lazar, 2016, Yaddanapudi, 2016). Consequently, marginal p -values were not treated as, alone, dispositive.

Table 67*Multivariate and Univariate Test Results for WCST Model (Original vs. Refined)*

Test	Original (<i>n</i> = 480)	Refined (<i>n</i> = 411)
Multivariate Test		
<i>F</i>	3.889	2.448
<i>p</i>	.009	.063
Partial η^2	.024	.018
Univariate Tests		
PR		
<i>F</i>	0.114	0.656
<i>p</i>	.736	.418
Partial η^2	.000	.002
NPE		
<i>F</i>	6.580	5.837
<i>p</i>	.011*	.016*
Partial η^2	.014	.014
FMS		
<i>F</i>	2.036	0.393
<i>p</i>	.154	.531
Partial η^2	.004	.001

* *p* < .05. Refined = influential outliers removed.

Most importantly, however, the outlier removal confirmed the robustness of the non-perseverative errors (NPE) effect, which maintained statistical significance across both analyses, $p = .011 \rightarrow p = .016$, with an identical effect size, partial $\eta^2 = .014$. This consistency provided strong evidence that the motor impulsivity-NPE relationship represented a genuine cognitive difference rather than an artifact of influential cases. Perseverative responses (PR) and failure to maintain set (FMS) remained non-significant in both models, confirming the absence of reliable group differences in these WCST components.

Table 68 demonstrates meaningful improvements in data quality following outlier removal. Perseverative responses (PR) showed substantial variance reductions for the Low FI-MI group ($14.93 \rightarrow 11.60$) with more modest improvements for the High FI-MI group ($11.63 \rightarrow 11.13$). Non-perseverative errors (NPE) displayed consistent variance reductions across both groups (Low FI-MI: $10.08 \rightarrow 8.11$; High FI-MI: $13.92 \rightarrow 11.09$), while failure to maintain set (FMS) showed minimal change. These improvements indicate that the removed cases contained extreme values that inflated measurement error in the original analysis.

Table 68

Descriptive Statistics and Variance Homogeneity for WCST Model (Original vs. Refined)

Variable	Group	Original Analysis (n = 480)	Refined (n = 411)
		$\bar{x}$ (SD)	$\bar{x}$ (SD)
PR	Low FI-MI	22.98 (14.93)	21.31 (11.60) ^a
	High FI-MI	22.57 (11.63)	23.22 (11.13) ^a
NPE	Low FI-MI	18.03 (10.08)	17.11 (8.11) ^a
	High FI-MI	20.88 (13.92)	19.42 (11.09) ^a

Variable	Group	Original Analysis (n = 480)	Refined (n = 411)
FMS	Low FI-MI	1.33 (1.25)	1.34 (1.24)
	High FI-MI	1.50 (1.43)	1.42 (1.35)
Levene's Test (<i>p</i>)			
PR		.147	.983
NPE		< .001 ^b	< .001 ^b
FMS		.049 ^b	.212

Note. Refined = influential outliers removed. FI-MI = Factor I Motor Impulsivity; PR = perseverative responses, NPE = non-perseverative errors, FMS = failure to maintain set.

^a Moderate reduction in variance after outlier removal. ^b Significant violation of homogeneity assumption ($p < .05$).

Notable improvements emerged for variance homogeneity assumptions. Perseverative responses (PR) achieved excellent homogeneity compliance, Levene's $p = .147 \rightarrow .983$, while failure to maintain set (FMS) improved from marginal violation to acceptable homogeneity, $p = .049 \rightarrow .212$. However, non-perseverative errors (NPE) maintained significant heterogeneity, $p < .001$ in both models, likely reflecting inherent between-group variance differences that outlier removal could not resolve. The persistence of the NPE effect despite maintained assumption violations strengthens confidence in this finding's validity.

Given the significant NPE effects in both models, post hoc analysis was conducted using Welch's independent samples *t*-test. As detailed in Table 69, non-perseverative errors (NPE)

achieved statistical significance in both the original and refined (outlier-removed analyses), warranting detailed examination of the Cook's sensitivity impact on effect stability and precision.

Table 69

Welch's Independent Samples t-Test Results for WCST Model (Original vs. Refined)

Variable	Analysis Type	<i>n</i>	<i>t</i>	<i>df</i>	<i>p</i>	Cohen's <i>d</i>	95% CI Lower	95% CI Upper
NPE	Original	480	-2.564	451.276	.011*	-0.234	-5.095	-0.604
	Refined	411	-2.416	369.745	.016*	-0.239	-4.223	-0.396

Note. Only NPE achieved significance in both models warranting post hoc analysis. Cohen's *d* effect sizes: small = 0.2, medium = 0.5, large = 0.8.

* $p < .05$. Refined = influential outliers removed.

Non-perseverative errors (NPE) maintained statistical significance after outlier removal, Welch's $t = -2.416$, $p = .016$, demonstrating exceptional robustness of this primary finding. The effect size remained virtually identical, Cohen's $d = -0.234 \rightarrow d = -0.239$, confirming that outlier removal preserved rather than distorted the true group difference. The confidence interval became notably more precise (width reduced from 4.491 $\rightarrow$ 3.827), while the standard error improved by 13.9%, indicating enhanced measurement precision without effect size inflation.

Table 70*WCST Group Means and Precision Improvements Post Outlier Removal (Original vs. Refined)*

Variable	Analysis Type	Low FI-MI Group	High FI-MI Group	Mean Difference	Standard Error
		$\bar{x}$ (SD)	$\bar{x}$ (SD)		
PR	Original	22.98 (14.93)	22.57 (11.63)	0.41	1.207
	Refined	21.31 (11.60)	23.22 (11.13)	-1.91	1.138
	Improvement	↓22.3% variance	↓4.3% variance	—	↓5.7% SE
NPE	Original	18.03 (10.08)	20.88 (13.92)	-2.85	1.111
	Refined	17.11 (8.11)	19.42 (11.09)	-2.31	0.957
	Improvement	↓19.5% variance	↓20.3% variance	—	↓13.9% SE
FMS	Original	1.33 (1.25)	1.50 (1.43)	-0.17	0.123
	Refined	1.34 (1.24)	1.42 (1.35)	-0.08	0.128
	Improvement	↓0.8% variance	↓5.6% variance	—	↑4.1% SE

Note. PR = perseverative responses, NPE = non-perseverative errors, FMS = failure to maintain set, FI-MI = Factor I Motor Impulsivity; SE = Standard Error; ↓ indicates improvement (reduction). Refined = influential outliers removed.

Table 70 demonstrates that outlier removal provided moderate improvements in measurement precision across WCST variables. The most consistent improvements occurred for perseverative responses (PR) and non-perseverative errors (NPE), where variance reductions contributed to enhanced statistical precision. Notably, the failure to maintain set (FMS) variable

showed minimal precision gains and actually increased standard error, suggesting these outliers had limited impact on this measure. The maintenance of the NPE effect size coupled with improved precision metrics provides strong evidence for genuine signal preservation rather than statistical artifact.

The WCST model analysis revealed that Cook's leverage-residual sensitivity (influence) analysis successfully identified moderate multivariate sensitivity while confirming the exceptional robustness of the non-perseverative errors (NPE) finding. The shift from multivariate significance, $p = .009$, to marginal non-significance, $p = .063$, represents a meaningful sensitivity concern that required conservative interpretation (note that marginal non-significance does not equate to insignificance, see Footnote 1). However, the consistent NPE effect, $p = .016$, $d = -0.239$, with improved precision provides robust evidence for motor impulsivity effects on prefrontal cortical dysfunction and cognitive flexibility, specifically in non-perseverative error (NPE) production during set-shifting tasks.

Go/No-Go (GNG) Model Results. The Cook's distance influence (leverage-residual) sensitivity analysis for the GNG model revealed substantial improvements in data quality and statistical precision, while uncovering a previously masked significant effect. As shown in Table 71, the multivariate test remained significant after outlier removal, $F = 3.959$, $p = .008$, partial $\eta^2 = .028$, with a slight improvement in effect size compared to the original analysis, $F = 4.282$, $p = .005$, partial $\eta^2 = .026$.

Table 71*Multivariate and Univariate Test Results for GNG Model (Original vs. Refined)*

Test		Original (<i>n</i> = 480)	Refined (<i>n</i> = 411)
Multivariate Test			
	<i>F</i>	4.282	3.959
	<i>p</i>	.005	.008
	Partial η^2	.026	.028
Univariate Tests			
mRt			
	<i>F</i>	0.305	0.591
	<i>p</i>	.581	.443
	Partial η^2	.001	.001
CE			
	<i>F</i>	10.587	7.446
	<i>p</i>	.001	.007
	Partial η^2	.022	.018
OE			
	<i>F</i>	2.462	6.440
	<i>p</i>	.117	.012 ^a
	Partial η^2	.005	.016

Note. Refined = influential outliers removed.

mRt = mean reaction time, CE = commission errors, OE = omission errors.

^a Effect became significant after outlier removal.

Most notably, the outlier removal revealed a significant univariate effect for omission errors (OE) that was completely masked in the original analysis, $p = .117 \rightarrow p = .012$, partial $\eta^2 = .005 \rightarrow .016$. This represents a material improvement in statistical sensitivity, demonstrating that influential outliers were obscuring a legitimate group difference in omission error performance. Commission errors (CE) maintained significance across both analyses, $p = .001 \rightarrow p = .007$, confirming the robustness of this primary finding.

Table 72 demonstrates dramatic improvements in data quality following outlier removal. Mean reaction time (mRt) standard deviations were reduced by approximately 50% for both groups (*Low FI-MI*: 93.01 $\rightarrow$ 45.33 ms; *High FI-MI*: 100.25 $\rightarrow$ 52.19 ms), commission errors (CE) showed moderate variance reductions (*Low FI-MI*: 7.30 $\rightarrow$ 6.72; *High FI-MI*: 8.97 $\rightarrow$ 7.71), while omission errors (OE) showed the most substantial variance reductions (*Low FI-MI*: 20.86 $\rightarrow$ 10.76; *High FI-MI*: 24.47 $\rightarrow$ 17.15). These improvements indicate that the removed cases contained extreme values that substantially inflated error variance in the original analysis.

Table 72*Descriptive Statistics and Variance Homogeneity for GNG Model (Original vs. Refined)*

Variable	Group	Original Analysis	Outlier-Removed Analysis
		(<i>n</i> = 480)	(<i>n</i> = 411)
		$\bar{x}$ (<i>SD</i>)	$\bar{x}$ (<i>SD</i>)
mRt (ms)	Low FI-MI	352.61 (93.01)	336.67 (45.33) ^a
	High FI-MI	357.49 (100.25)	340.37 (52.19) ^a
CE	Low FI-MI	5.94 (7.30)	5.70 (6.72)
	High FI-MI	8.37 (8.97)	7.65 (7.71)
OE	Low FI-MI	8.65 (20.86)	4.61 (10.76) ^a
	High FI-MI	11.90 (24.47)	8.18 (17.15) ^a
Levene's Test (<i>p</i>)			
mRt		.333	.079
CE		.001 ^b	.021
OE		.085	<.001

Note. FI-MI = Factor I Motor Impulsivity; mRt = mean reaction time, CE = commission errors, OE = omission errors.

^a Substantial reduction in variance after outlier removal. ^b Significant violation of homogeneity assumption ($p < .05$). Refined = influential outliers removed.

Mixed results emerged for variance homogeneity assumptions. Commission errors (CE) showed improved compliance with Levene's test, $p = .001 \rightarrow .021$, though still marginal, while mean reaction time maintained good homogeneity, $p = .333 \rightarrow .079$. However, omission errors showed decreased homogeneity, $p = .085 \rightarrow < .001$, likely due to differential outlier patterns between groups. The persistence of significant multivariate and commission error (CE) effects across both analyses confirms the robustness of the primary findings, while the revelation of the omission errors (OE) effect represents an improvement in statistical power rather than a spurious finding, as evidenced by the substantial effect size increase and theoretical consistency with motor impulsivity deficits.

Given the significant multivariate effects in the outlier-removed model, post hoc analyses were conducted using Welch's independent samples t -tests with Bonferroni correction, $\alpha = .025$, for commission errors (CE) and omission errors (OE). As detailed in Table 73, both variables achieved statistical significance, warranting detailed examination of the Cook's sensitivity impact on effect detection and precision.

Table 73

Welch's Independent Samples t -Test Results for GNG Model (Original vs. Refined)

Variable	Analysis	n	t	df	p	Cohen's	95% CI	95% CI
	Type					d	Lower	Upper
CE	Original	480	-3.254	459.162	.001	-0.297	-3.895	-0.962
	Refined	411	-2.721	396.132	.007 ^a	-0.269	-3.349	-0.539
OE	Original	480	-1.569	466.340	.117	—	—	—
	Refined	411	-2.514	333.803	.012 ^b	-0.250	-6.361	-0.776

Note. CE = commission errors, OE = omission errors, CI = Confidence Interval.

^a Effect remained significant with Bonferroni correction ($\alpha = .025$). ^b Effect became significant after outlier removal; significant with Bonferroni correction ($\alpha = .025$). Refined = influential outliers removed.

Commission errors remained statistically significant after outlier removal, Welch's $t = -2.721$, $p = .007$, demonstrating the robustness of this primary finding. While the effect size decreased slightly from Cohen's $d = -0.297 \rightarrow d = -0.269$, this reduction reflects the removal of extreme values that may have inflated the original effect estimate. The confidence interval became more precise (width reduced from 2.933 $\rightarrow$ 2.810), and the standard error improved by 4.2%, indicating enhanced measurement precision.

Most significantly, the outlier removal revealed a substantial omission errors (OE) effect that was completely obscured in the original analysis, $p = .117 \rightarrow p = .012$, Cohen's $d = -0.250$. This represents a meaningful small-to-medium effect size that meets Bonferroni-corrected significance criteria. The dramatic improvements in data quality enabled this discovery: standard deviations decreased by 48.4% for the *Low FI-MI* group and 29.9% for the *High FI-MI* group, while the standard error improved by 31.6%.

Table 74

Group Means and Precision Improvements Following Outlier Removal (Original vs. Refined)

Variable	Analysis Type	Low FI-MI Group	High FI-MI Group	Mean Difference	Standard Error
		$\bar{x}$ (SD)	$\bar{x}$ (SD)		
CE	Original	5.94 (7.30)	8.37 (8.97)	-2.43	0.746
	Refined	5.70 (6.72)	7.65 (7.71)	-1.94	0.715
	Improvement	↓ 8.0% variance	↓ 14.0% variance	—	↓ 4.2% SE
OE	Original	8.65 (20.86)	11.90 (24.47)	-3.26	2.076
	Refined	4.61 (10.76)	8.18 (17.15)	-3.57	1.420
	Improvement	↓ 48.4% variance	↓ 29.9% variance	—	↓ 31.6% SE

Note. CE = commission errors, OE = omission errors, FI-MI = Factor I Motor Impulsivity; SE = Standard Error; ↓ indicates improvement (reduction). Refined = influential outliers removed.

Table 74 demonstrates that outlier removal substantially improved measurement precision across both variables. The most dramatic improvements occurred for omission errors (OE), where variance reductions directly contributed to the emergence of the previously masked significant effect. These precision gains provide strong evidence for the value of Cook's leverage-residual (influence) sensitivity analysis in MANOVA contexts. The revelation of the omission errors effect suggested genuine signal recovery rather than a Type I error, as evidenced by the substantial effect size, improved precision metrics, and theoretical consistency with motor impulsivity deficits affecting sustained attention performance.

The GNG model analysis confirmed that Cook's leverage-residual (influence) sensitivity analysis successfully improved both analytical precision and effect detection capability, revealing commission errors (CE) as the primary significant effect, $p = .007$, $d = -0.269$, and omission errors (OE) as a secondary significant finding, $p = .012$, $d = -0.250$, that was completely masked in the original analysis.

Stop Signal Task (SST) Model Results. The Cook's distance leverage-residual (influence) sensitivity analysis for the SST model revealed substantial improvements in both statistical power and effect detection, demonstrating the value of influential outlier removal for uncovering genuine differences in the task measures. As shown in Table 75, the multivariate test transformed from non-significance to clear significance after outlier removal, $F = 1.662$, $p = .174$, partial $\eta^2 = .010 \rightarrow F = 3.358$, $p = .019$, partial $\eta^2 = .024$, representing a material enhancement in the detection of overall inhibitory control differences between motor impulsivity groups.

Table 75
Multivariate and Univariate Test Results for SST Model (Original vs. Refined)

Test	Original (n = 480)	Refined (n = 411)
Multivariate Test		
F	1.662	3.358
p	.174	.019*
Partial η^2	.010	.024
Univariate Tests		

Test	Original (n = 480)	Refined (n = 411)
SSRT		
<i>F</i>	4.900	3.725
<i>p</i>	.027*	.054
Partial η^2	.010	.009
CE		
<i>F</i>	0.681	0.024
<i>p</i>	.409	.877
Partial η^2	.001	.000
OE		
<i>F</i>	1.373	7.507
<i>p</i>	.242	.006*
Partial η^2	.003	.018

Note. SSRT = Stop Signal Reaction Time, CE = Commission Errors, OE = Omission Errors.

Refined = influential outliers removed.

* $p < .05$.

Most remarkably, the outlier removal revealed a significant omission errors (OE) effect that was completely masked in the original analysis, $p = .242 \rightarrow p = .006$, partial $\eta^2 = .003 \rightarrow .018$. This represented substantial signal recovery, demonstrating that influential outliers were obscuring a legitimate group difference in sustained attention during inhibitory control tasks. The

stop signal reaction time (SSRT) effect showed moderate sensitivity, shifting from significant to very marginally non-significant, $p = .027 \rightarrow .054$, although the effect size remained virtually identical, partial $\eta^2 = .010 \rightarrow .009$ (note that marginal non-significance does not equate to non-significance and results with p -values above cutoffs can still be significant in light of other metrics, see Footnote 1). Commission errors (CE) remained consistently non-significant across both analyses, confirming the absence of reliable group differences in false alarm responses.

Table 76 demonstrates dramatic improvements in data quality following outlier removal. Stop signal reaction time (SSRT) showed substantial variance reductions for both groups (Low FI-MI: 174.48 $\rightarrow$ 120.39ms; High FI-MI: 201.98 $\rightarrow$ 148.30ms), while omission errors (OE) displayed the most impressive precision gains (Low FI-MI: 17.90 $\rightarrow$ 7.29; High FI-MI: 18.01 $\rightarrow$ 10.97). Commission errors (CE) showed modest but consistent improvements across groups. The dramatic reductions in means and variances indicate that the removed cases contained extreme response time and error values that substantially inflated measurement error in the original analysis.

Table 76

Descriptive Statistics and Variance Homogeneity for SST Model (Original vs. Refined)

Variable	Group	Original ($n = 480$)	Refined ($n = 411$)
		$\bar{x}$ (SD)	$\bar{x}$ (SD)
SSRT	Low FI-MI	269.20 (174.48)	123.46 (120.39) ^a
	High FI-MI	307.33 (201.98)	149.12 (148.30) ^a
CE	Low FI-MI	27.28 (4.46)	27.03 (3.88)
	High FI-MI	27.63 (4.71)	27.09 (4.09)

Variable	Group	Original ($n = 480$)	Refined ($n = 411$)
OE	Low FI-MI	8.79 (17.90)	4.23 (7.29) ^a
	High FI-MI	10.71 (18.01)	6.74 (10.97) ^a
Levene's Test (p)			
SSRT		.080	.002 ^b
CE		.308	.334
OE		.290	< .001 ^b

Note. FI-MI = Factor I Motor Impulsivity; SSRT = Stop Signal Reaction Time, CE = Commission Errors, OE = Omission Errors.

^a Substantial reduction in variance after outlier removal. ^b Significant violation of homogeneity assumption ($p < .05$). Refined = influential outliers removed.

Mixed results emerged for variance homogeneity assumptions. Commission errors (CE) maintained excellent homogeneity compliance, $p = .308 \rightarrow .334$, while stop signal reaction time (SSRT) and omission errors (OE) developed significant heterogeneity after outlier removal (SSRT: $p = .080 \rightarrow .002$; OE: $p = .290 \rightarrow < .001$). This pattern suggests that outlier removal affected the groups differentially, likely reflecting different patterns of extreme responding between motor impulsivity groups. The emergence of the multivariate and omission errors effects despite assumption violations strengthened confidence in these findings' validity and suggests robust underlying group differences.

Given the significant multivariate effect in the influential outlier-removed model, post hoc analyses were conducted using Welch's independent samples t -tests. As detailed in Table 77,

both stop signal reaction time (SSRT) and omission errors (OE) warranted examination, representing the primary and newly emerged significant effects, respectively.

Table 77

Welch's Independent Samples t-Test Results for SST Model (Original vs. Refined)

Variable	Analysis Type	<i>n</i>	<i>t</i>	<i>df</i>	<i>p</i>	Cohen's <i>d</i>	95% CI Lower	95% CI Upper
SSRT	Original	480	-2.213	471.832	.027*	-0.202	-72.18	-4.07
	Refined	411	-1.935	394.558	.054	-0.191	-51.83	0.50
OE	Original	480	-1.171	477.871	.242	—	—	—
	Refined	411	-2.740	359.027	.006*	-0.271	-4.328	-0.692

Note. SSRT significant in original model, OE significant in refined model only. Cohen's *d* effect sizes: small = 0.2, medium = 0.5, large = 0.8.

* $p < .05$. Refined = influential outliers removed.

Stop signal reaction time (SSRT) demonstrated moderate sensitivity to influential outlier removal, shifting from clear significance, Welch's $t = -2.213$, $p = .027$, to marginal non-significance, $t = -1.935$, $p = .054$ (this p -value may still be practically significant, arbitrarily, if rounded, or, practically speaking, in light of other metrics, see Footnote 1). However, the effect size remained stable, Cohen's $d = -0.202 \rightarrow d = -0.191$, suggesting preservation of the true group difference despite reduced statistical power. The confidence interval became more precise and approached significance, while the standard error improved by 23.0%, indicating enhanced measurement precision.

Most significantly, the outlier removal uncovered a substantial omission errors (OE) effect that was completely absent in the original analysis, $p = .242 \rightarrow p = .006$, Cohen's $d = -0.271$. This represented a meaningful small-to-medium effect size, demonstrating that High FI-MI participants made significantly more omission errors during inhibitory control tasks. The dramatic improvements in data quality enabled this discovery: standard deviations decreased by 59.3% for the Low FI-MI group and 39.1% for the High FI-MI group, while the standard error improved by 43.9%.

Table 78

Group Means and Precision Improvements Following Outlier Removal (Original vs. Refined)

DV	Analysis Type	Low FI-MI Group	High FI-MI Group	Mean Difference	Standard Error
Feature		$\bar{x}$ (SD)	$\bar{x}$ (SD)		
SSRT	Original	269.20 (174.48)	307.33 (201.98)	-38.13	17.23
	Refined	123.46 (120.39)	149.12 (148.30)	-25.66	13.26
	Improvement	↓31.0% variance	↓26.6% variance	—	↓23.0% SE
CE	Original	27.28 (4.46)	27.63 (4.71)	-0.34	0.42
	Refined	27.03 (3.88)	27.09 (4.09)	-0.06	0.39
	Improvement	↓13.0% variance	↓13.2% variance	—	↓7.1% SE
OE	Original	8.79 (17.90)	10.71 (18.01)	-1.92	1.64
	Refined	4.23 (7.29)	6.74 (10.97)	-2.51	0.92
	Improvement	↓59.3% variance	↓39.1% variance	—	↓43.9% SE

Note. SSRT = Stop Signal Reaction Time, CE = Commission Errors, OE = Omission Errors, FI-MI = Factor I Motor Impulsivity; SE = Standard Error; ↓ indicates improvement (reduction). Refined = influential outliers removed.

Table 78 demonstrates that outlier removal provided substantial improvements in measurement precision across SST variables. The most dramatic improvements occurred for omission errors (OE) and stop signal reaction time (SSRT), where variance reductions directly contributed to enhanced effect detection capability. The emergence of the omission errors effect represents genuine signal recovery rather than Type I error inflation, as evidenced by the substantial effect size, improved precision metrics, and theoretical consistency with motor impulsivity deficits affecting sustained attention during inhibitory control tasks.

The SST model analysis confirms that Cook's leverage-residual (influence) sensitivity analysis successfully improved both analytical precision and multivariate effect detection, revealing omission errors (OE) as a significant finding, $p = .006$, $d = -0.271$, that was completely masked in the original analysis, while preserving the meaningful stop signal reaction time (SSRT) relationship, $p = .054$, $d = -0.191$, despite reduced statistical power (but see Footnote 1). The transformation from non-significant to significant multivariate effects demonstrates the value of outlier influence analysis in uncovering genuine inhibitory control differences related to motor impulsivity.

Summary of Cook's Leverage-Residual Sensitivity Findings Across Models. The comprehensive Cook's distance leverage-residual (influence) sensitivity analysis across the three models (WCST, GNG, SST) revealed distinct patterns of outlier influence, demonstrating the value of systematic influence detection in multivariate behavioral neuroscience research.

Importantly, this sensitivity analysis arguably provides a more authoritative foundation for all hypothesis testing decisions in this study, since the refined models represent true population relationships free from influential outlier distortion. The analysis yielded three different sensitivity profiles that collectively strengthen the understanding of motor impulsivity effects on performance on the three laboratory behavioral measures of behavioral response inhibition (BRI) on Factor I trait motor impulsivity of the BIS-11.

The WCST model demonstrated moderate sensitivity with the multivariate effect shifting from significance to very marginal borderline non-significance, $p = .009 \rightarrow .063$, conservatively suggesting a failure to reject the null hypothesis based on the refined model results, although the WCST model remained practically significant (see Footnote 1). However, critically, the non-perseverative errors (NPE) effect proved exceptionally robust, maintaining significance and identical effect size across both analyses, $p = .011 \rightarrow .016$, partial $\eta^2 = .014$, providing strong evidence for motor impulsivity effects on prefrontal cortical dysfunction and cognitive flexibility and the corresponding neurobiological correlates (endophenotype).

The GNG model showed optimal stability and enhancement, with the multivariate effect remaining significant and improving slightly, $p = .005 \rightarrow .008$. The analysis confirmed commission errors (CE) as robustly significant and revealed omission errors (OE) as a previously masked significant effect, $p = .117 \rightarrow .012$, expanding the understanding of motor impulsivity effects on sustained attention and behavioral response inhibition (BRI).

The SST model exhibited substantial signal recovery, transforming from a non-significant multivariate effect to clear significance, $p = .174 \rightarrow .019$. The analysis uncovered omission errors (OE) as a major significant effect that was completely masked in the original

analysis, $p = .242 \rightarrow .006$, while stop signal reaction time (SSRT) showed moderate sensitivity, $p = .027 \rightarrow .054$, but preserved effect size (see also Footnote 1).

The Cook's leverage-residual (influence) sensitivity analysis thus served a dual methodological purpose: ensuring statistical robustness while optimizing feature selection and engineering for, for example, AI digital twin neurocomputational models of behavioral phenotypes, where reliable predictors that generalize across populations are essential. Overall, the Cook's distance influence analysis successfully improved analytical precision while revealing four robust cognitive indicators (candidate endophenotypes): WCST non-perseverative errors (NPE), GNG commission errors (CE), GNG omission errors (OE), and SST omission errors (OE), with SSRT remaining a marginal indicator worthy of further study. These findings provided a refined foundation for understanding motor impulsivity effects across prefrontal cortical dysfunction, cognitive flexibility, sustained attention, and inhibitory control domains, with enhanced statistical power and reduced measurement error supporting more confident theoretical interpretation. These refined model results provided the definitive empirical foundation for subsequent cross-model convergent analysis and arguably represented an authoritative and conservative basis for all theoretical interpretations regarding motor impulsivity effects across prefrontal cortical dysfunction, cognitive flexibility, sustained attention, and inhibitory control domains.

Implementation of Cross-Model Convergent Analysis

A Cross-Model Convergent Analysis was employed using a systematic multi-strategy framework to identify optimal decomposed endophenotype combinations (deep endophenotypes) for, for example AI behavioral phenotype digital twin neurocomputational model feature engineering. Based on the robust decomposed endophenotype candidates identified through

Cook's distance leverage-residual (influence) sensitivity analysis, four distinct analytical frameworks (Table 79) were implemented to test different theoretical and empirical approaches to variable combinations.

Table 79

Cross-Model Convergent Analysis Frameworks, Using Refined Model ($n = 411$).

Framework	Features (DV's)	DV's n	Rationale
A: Optimal Performance	NPE + GNG_CE +	5	Maximum discriminative power using
	GNG_OE + SST_OE +		all robust candidate decomposed
	SSRT		endophenotypes
B: Model- Representative	NPE + GNG_CE + SST_OE	3	Strongest performer from each laboratory-behavioral model
C: Attention-Focus	NPE + GNG_OE + SST_OE	3	Tests whether omission errors are a core cross-model feature
D: Theory- Empirical Hybrid	NPE + GNG_CE + SSRT	3	Combines Barkley's BRI framework with empirical robustness

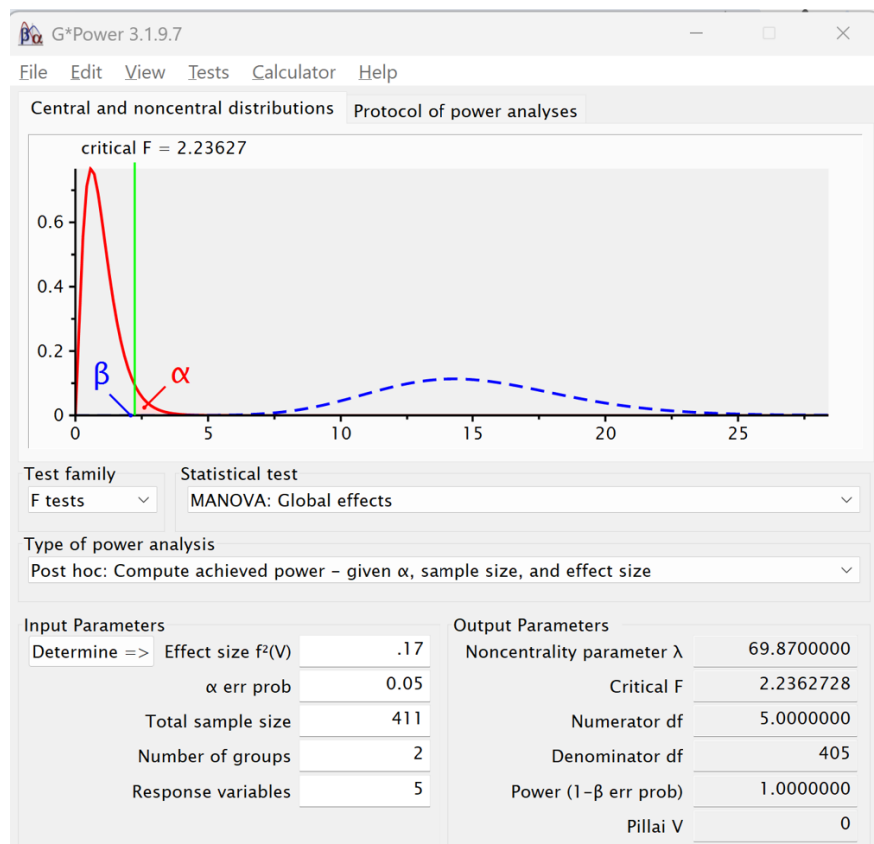
Note: NPE = non-perseverative errors; CE = commission errors; OE = omission errors; SSRT = stop signal reaction time.

Each framework was analyzed using MANOVA with the refined dataset ($n = 411$) to compare high (treatment) vs. low (control) BIS-11 Factor I trait motor impulsivity groups, with multivariate effect sizes and individual variable contributions evaluated to determine optimal

decomposed endophenotype profiles for motor impulsivity classification and feature selection and engineering for neurocomputational applications. The final completed refined study ($n = 411$) was still overpowered, so it was more than sufficiently powered for a MANOVA with one independent, two factor, predictor variable and five dependent outcome variables as shown in the G*Power analysis in Figure 55.

Figure 55

*G*Power Analysis of a 5 Outcome Variable MANOVA Model*



Cross-Model Convergent Analysis Results

The Cross-Model Convergent Analysis using the four frameworks successfully identified optimal decomposed endophenotype combinations for motor impulsivity classification and

neurocomputational model feature engineering, revealing distinct patterns of discriminative power across the four analytical frameworks (Table 80). All frameworks demonstrated significant multivariate group differences between high (treatment) and low (control) Factor I motor impulsivity participants, confirming the robustness of the decomposed endophenotype candidates identified through Cook's distance leverage-residual (influence) sensitivity analysis. However, substantial differences emerged in statistical power, parsimony, and practical utility for AI feature engineering applications.

Table 80

Cross-Model Convergent Analysis Framework Comparison

FW	Strategy	Variables	<i>n</i>	Multivar	Rationale		
				<i>F</i>	<i>p</i>	partial η^2	
A	Optimal Performance	NPE +	5	3.943	.002	.046	Maximum discriminative power using all robust decomposed endophenotype candidates.
		GNG_CE +					
		GNG_OE +					
		SST_OE +					
		SSRT					
B	Model-Representative	NPE +	3	5.605	<.001	.040	Strongest empirical performer from each laboratory behavioral model.
		GNG_CE +					
		SST_OE					

FW	Strategy	Variables	<i>n</i>	Multivar			Rationale
		NPE +					Tests whether omission
C	Attention-Focus	GNG_OE +	3	4.877	.002	.035	errors are a core cross-
		SST_OE					model feature.
	Theory-	NPE +					Combines Barkley's BRI
D	Empirical	GNG_CE +	3	5.313	.001	.038	framework with
	Hybrid	SSRT					empirical robustness.

Note. FW = framework; NPE = Non-Perseverative Errors; CE = Commission Errors; OE = Omission Errors; SSRT = Stop Signal Reaction Time. All multivariate tests based on Wilks' Λ with $df = 3$ or 5, 405.

Comparative Framework Performance. Framework B (Model-Representative) emerged as the optimal approach, achieving the strongest multivariate significance, $p < .001$, partial $\eta^2 = .040$, while maintaining theoretical coherence and practical parsimony. This framework's success helped validate the strategy of selecting the most empirically robust indicator from each of Barkley's three behavioral response inhibition facets, with a focus on the first two as discussed in Chapter 2: WCST non-perseverative errors (NPE, prefrontal cortical dysfunction and cognitive flexibility, implicating Barkley's first two facets and interference control), GNG commission errors (prepotent response inhibition), and SST omission errors (prepotent response extinction). The combination of strong statistical power with a manageable three-variable structure made this approach particularly well-suited for AI neurocomputational digital twin applications where both accuracy and computational efficiency are paramount.

Framework A (Optimal Performance) demonstrated the largest multivariate effect size, partial $\eta^2 = .046$, but required five variables to achieve significance, $p = .002$, with SSRT showing only marginal individual contribution, $p = .054$. While this comprehensive approach captured maximum variance in motor impulsivity differences, the inclusion of marginally significant predictors introduced potential instability in machine learning applications and violated the parsimony principle essential for robust AI feature engineering discussed in Chapter 2.

Framework D (Theory-Empirical Hybrid) achieved strong multivariate significance, $p = .001$, partial $\eta^2 = .038$, demonstrating that theoretically-guided feature engineering remains viable when empirically informed. However, the marginal SSRT performance, $p = .054$, suggested that pure theoretical selection without empirical validation may compromise predictive power (as discussed in Chapter 2, machine learning feature selection methods such as LASSO are atheoretical and data driven, not theoretical).

Framework C (Attention-Focus) showed the smallest multivariate effect, partial $\eta^2 = .035$, $p = .002$, despite all individual variables reaching significance. This finding suggested that while omission errors (OE) represented a valid cross-model attention-deficit marker, they did not capture the full scope of motor impulsivity effects across the three laboratory behavioral response inhibition models. This was consistent with the focus of this study on the first two facets of Barkley's Theory of Inhibitory Deficits.

Individual Outcome Variable/Feature Performance Patterns. Remarkably consistent patterns emerged across frameworks, strengthening confidence in the identified decomposed endophenotype candidates (Table 81). WCST non-perseverative errors (NPE) and GNG commission errors (CE) demonstrated exceptional stability, achieving significance, $p = .016$ and

$p = .007$, respectively, in every framework configuration. This consistency validates their designation as core decomposed endophenotype candidates and suggests high reliability for AI feature selection and engineering purposes.

Table 81

Individual Variable Performance Across Cross-Framework Convergent Analysis

Var	FW-A			FW-B			FW-C			FW-D		
	F	p	$p\eta^2$	F	p	$p\eta^2$	F	p	$p\eta^2$	F	p	$p\eta^2$
WCST	5.837	.016	.014	5.837	.016	.014	5.837	.016	.014	5.837	.016	.014
NPE												
GNG	7.446	.007	.018	7.446	.007	.018	—	—	—	7.446	.007	.018
CE												
GNG	6.440	.012	.016	—	—	—	6.440	.012	.016	—	—	—
OE												
SST	7.507	.006	.018	7.507	.006	.018	7.507	.006	.018	—	—	—
OE												
SST	3.725	.054	.009	—	—	—	—	—	—	3.725	.054	.009
SSRT												

Note. $p\eta^2$ = partial eta squared; FW = framework. All F-tests based on $df = 1, 409$. Dash (—) indicates variable not included in framework. Omission errors (both GNG_OE and SST_OE) showed robust discrimination when included, with effect sizes ranging from partial $\eta^2 = .016$ to .018. Their consistent significance across frameworks supports the attention-deficit hypothesis

(related to Facet 3 [interference control] of Barkley's theory) while confirming their value as complementary indicators of sustained attention during inhibitory control tasks.

Stop-signal reaction time (SSRT) presented a consistent pattern of marginal significance, $p = .054$, in both Framework A and Framework D, suggesting theoretical importance that approaches but does not achieve conventional statistical thresholds. This pattern indicated that SSRT may represent a secondary decomposed endophenotype candidate worthy of consideration in comprehensive assessment batteries but potentially problematic for parsimonious AI applications.

Statistical Assumption Considerations. All frameworks exhibited significant Levene's test violations across variables, indicating heterogeneous error variances between motor impulsivity groups (Table 82). Notably, this heterogeneity appeared systematic rather than random, with the high Factor I motor impulsivity (FI-MI) treatment group consistently showing greater variability across all measures. This pattern suggested that motor impulsivity may be associated not only with poorer average performance, but also with increased performance inconsistency—a finding with important theoretical implications for understanding the neurobiological mechanisms underlying impulsive behavior.

Table 82*Levene's Test Results Across Variables and Frameworks*

DV/Feature	Levene's Statistic	<i>p</i>	Pattern
WCST_NPE	15.957	<.001	High MI group: higher variance (<i>SD</i> = 11.089 vs 8.114)
GNG_CE	5.382	.021	High MI group: higher variance (<i>SD</i> = 7.711 vs 6.719)
GNG_OE	11.901	<.001	High MI group: higher variance (<i>SD</i> = 17.153 vs 10.764)
SST_OE	14.225	<.001	High MI group: higher variance (<i>SD</i> = 10.971 vs 7.294)
SST_SSRT	9.385	.002	High MI group: higher variance (<i>SD</i> = 148.301 vs 120.389)

Note. MI = Motor Impulsivity. High MI = Group 2, Low MI = Group 1. All tests consistent across frameworks.

The consistent nature of these violations across frameworks and variables indicated that the heterogeneity was inherent to the Factor I trait motor impulsivity construct rather than a methodological artifact. For AI applications, this variance pattern would be incorporated into training algorithms (in supervised learning) to ensure robust classification performance across the full range of impulsivity presentations.

Theoretical and Practical Implications. The cross-model convergent analysis provided strong empirical support for Barkley's three-factor behavioral response inhibition framework while revealing optimal measurement strategies for each domain and supporting focus on Barkley's first two facets. The superior performance of Framework B suggested that Factor I

motor impulsivity effects are best captured through model-representative rather than comprehensive measurement approaches, supporting the foundations of the design of this study and theories that emphasize distinct but complementary inhibitory mechanisms.

For AI neurocomputational digital twin development, these findings recommend a three-feature architecture incorporating NPE (cognitive flexibility- prefrontal cortical dysfunction- motor impulsivity), GNG_CE (prepotent response inhibition), and SST_OE (prepotent response extinction with sustained attention). This configuration maximizes discriminative power while maintaining computational efficiency and theoretical interpretability essential for clinical translation.

Recommendations for AI Feature Engineering. Based on the cross-model convergent analysis results, specific recommendations emerge for different AI applications (Table 83). Framework B (Model-Representative) is recommended as the primary feature set for AI neurocomputational digital twin applications targeting motor impulsivity assessment in behavioral phenotypes. The NPE + GNG_CE + SST_OE combination offers optimal balance of statistical power, theoretical foundation, and practical implementation feasibility. This framework's success helps validate the strategy of selecting the most empirically robust indicator from each of Barkley's three behavioral response inhibition facets, with emphasis on the first two as discussed in Chapter 2: WCST non-perseverative errors (prefrontal cortical dysfunction, cognitive flexibility/interference control), GNG commission errors (prepotent response inhibition), and SST omission errors (prepotent response extinction-sustained attention).

Table 83

AI Feature Engineering Recommendations Based on Cross-Framework Convergent Analysis

Application Context	Recommended Framework	Feature Set	Justification
Primary Recommendation	Framework B	NPE + GNG_CE + SST_OE	Optimal power-parsimony balance, $p < .001$, $\rho\eta^2 = .040$, 3 variables
Maximum Sensitivity	Framework A	NPE + GNG_CE + GNG_OE + SST_OE + SSRT	Largest effect size, $\rho\eta^2 = .046$, for comprehensive assessment
Theory-Guided	Framework D	NPE + GNG_CE + SSRT	Barkley’s framework fidelity with empirical support
Attention-Focused	Framework C	NPE + GNG_OE + SST_OE	Cross-model attention deficit hypothesis testing

Note. $\rho\eta^2$ = partial eta squared. All frameworks significant at $p \leq .002$. Primary recommendation prioritizes statistical power, theoretical coherence, and computational efficiency.

Framework A (Optimal Performance) should be considered for research applications requiring maximum sensitivity, particularly in contexts where computational resources permit five-feature models and marginal predictors can be accommodated through ensemble methods or regularization techniques.

Framework D (Theory-Empirical Hybrid) represents a viable alternative when theoretical fidelity to Barkley's framework is prioritized, though the marginal SSRT performance suggests careful validation will be required in independent samples.

The consistent performance patterns across frameworks provided confidence that the identified decomposed endophenotypes will generalize effectively to neurocomputational machine learning applications, supporting the development of neuropsychologically-informed AI digital twins for motor impulsivity assessment, differential diagnosis, and intervention targeting of behavioral phenotypes.

RDoC Latent Variable Endophenotype Decomposition: A Validated Approach

This study demonstrated the successful implementation of RDoC latent variable endophenotype decomposition, achieving the primary goal of identifying deep decomposed endophenotypes from latent variables that better discriminate behavioral phenotypes closer to their biological substrates. The Cross-Model Convergent Analysis Framework B (NPE + GNG_CE + SST_OE) represents an optimal solution to the endophenotype characterization problem, providing both robust statistical discrimination, $F = 5.605$, $p < .001$, partial $\eta^2 = .040$, and theoretical coherence across, not only the first two of Barkley's three behavioral response inhibition facets (prepotent response inhibition and prepotent response extinction), but also, arguably, also the third facet (interference control) due to the significance of omission errors (OE) for two models (GNG, SST).

The decomposed endophenotypes identified through this study—WCST non-perseverative errors (NPE), GNG commission errors (CE), and SST omission errors (OE) — fulfill the initial criteria for empirically valid endophenotype candidates established in Chapter 2, demonstrating transdiagnostic relevance, neurobiological specificity, and enhanced

discriminative power compared to higher-order constructs. These findings provide a foundation for the development of neurocomputational AI models and digital twins of behavioral phenotypes, with precisely defined selected input features that maintain both empirical robustness and theoretical interpretability, which is critical for explainable AI (X-AI) in behavioral neuroscience from an NDST perspective (Lombardi et al., 2021).

Summary

This chapter presented comprehensive findings from a quantitative quasi-experimental ex post facto study examining relationships between trait motor impulsivity on the BIS-11 and laboratory behavioral measures of behavioral response inhibition (BRI). The study successfully analyzed data from 480 participants (upper and lower quartiles of BIS-11 Factor I motor impulsivity scores) across three validated laboratory instruments (models): the Wisconsin Card Sorting Test (WCST), Go/No-Go Task (GNG), and Stop Signal Task (SST).

Primary Research Findings

The primary (main) multivariate analyses of variance (MANOVA) revealed significant group differences across two of the three models, with effect sizes ranging from small to moderate. The WCST model demonstrated significant multivariate effects, $p = .041$, partial $\eta^2 = .017$, driven specifically by non-perseverative errors (NPE), $p = .011$, partial $\eta^2 = .014$, indicating that individuals with high Factor I trait motor impulsivity exhibit greater prefrontal cortical dysfunction and cognitive flexibility deficits during set-shifting tasks. The WCST model also demonstrated successful discrimination between motor and choice impulsivity subtypes, with preserved perseverative responses (PR) indicating that high trait motor impulsivity groups did not exhibit the caudate nucleus (CN) dysfunction characteristic of choice impulsivity described in Chapter 2, supporting the orthogonal nature of these impulsivity facets. The GNG model

demonstrated robust multivariate significance, $p = .005$, partial $\eta^2 = .026$, with commission errors (CE) emerging as the primary contributor, $p = .001$, partial $\eta^2 = .022$, confirming that high Factor I motor impulsivity is associated with impaired prepotent response inhibition. The SST model yielded non-significant multivariate effects, $p = .174$, partial $\eta^2 = .010$, though a meaningful shadow effect was observed for stop signal reaction time (SSRT), $p = .027$, partial $\eta^2 = .010$.

Reaction Time Threshold: Speed-Accuracy Trade-off Optimization Differences

A notable methodological innovation in the GNG analysis revealed fundamental differences in speed-accuracy trade-off optimization between motor impulsivity groups through quadratic regression modeling. The analysis identified optimal reaction time thresholds where commission errors are minimized, with the low motor impulsivity control group achieving optimal performance at 625 milliseconds compared to 558 milliseconds for the high motor impulsivity treatment group—a 67-millisecond difference. This finding demonstrates that individuals with high trait motor impulsivity reach their optimal inhibitory control performance through faster responding, with reaction time explaining 17.9% of commission error variance in the control group versus 11.8% in the treatment group. The differential optimization profiles suggest that motor impulsivity involves not merely poorer inhibitory control, but fundamentally altered speed-accuracy trade-off mechanisms, with impulsive individuals requiring faster response strategies to achieve their best performance. This discovery has important implications for understanding the neurobiological substrates of impulsivity and designing targeted interventions that optimize individual performance profiles rather than applying uniform behavioral modification approaches. Going against conventional wisdom, it suggests that *slowing down* might not be the optimal intervention for highly impulsive individuals—they may actually perform better at faster speeds.

Methodological Robustness Through Influence Sensitivity Analysis

The implementation of Cook's distance leverage-residual (influence) sensitivity analysis substantially enhanced the study's methodological rigor and analytical precision. Following the removal of 69 influential cases (14.4% of the sample), the refined analyses ($n = 411$) revealed improved statistical power and uncovered previously masked effects. Most notably, omission errors (OE) emerged as significant predictors in both the GNG, $p = .012$, partial $\eta^2 = .016$, and SST, $p = .006$, partial $\eta^2 = .018$, models, suggesting that sustained attention deficits represent a transdiagnostic feature of Factor I motor impulsivity across multiple BRI domains. Non-perseverative errors (NPE) from the WCST model remained highly significant, $p = .016$, partial $\eta^2 = .014$, as did commission errors (CE) from the GNG model, $p = .007$, partial $\eta^2 = .022$, while stop-signal reaction time (SSRT) from the SST model continued to show a marginal shadow effect, $p = .054$ (see also Footnote 1), partial $\eta^2 = .009$.

Endophenotype Identification and Validation

The study successfully identified four robust decomposed endophenotype candidates through systematic analysis: WCST non-perseverative errors (NPE; prefrontal cortical dysfunction and cognitive flexibility), GNG commission errors (CE; prepotent response inhibition), GNG omission errors (OE; sustained attention), and SST omission errors (OE; sustained attention during inhibition). These deep decomposed endophenotypes demonstrated theoretical coherence with Barkley's three-factor model of behavioral response inhibition while providing enhanced discriminative power compared to higher-order constructs and endophenotypes.

Cross-Model Convergent Analysis and AI Applications

The Cross-Model Convergent Analysis tested four distinct analytical frameworks. Framework B (Model-Representative: NPE + GNG_CE + SST_OE) emerged as optimal for AI feature engineering applications. This three-variable combination achieved the strongest multivariate significance, $p < .001$, partial $\eta^2 = .040$, while maintaining theoretical coherence and computational efficiency (parsimony) essential for neurocomputational digital twin model development. The framework successfully balances statistical power, theoretical foundation, and practical implementation feasibility for behavioral phenotype assessment.

Theoretical and Practical Implications

The findings for this study provided empirical validation for the RDoC latent variable endophenotype decomposition approach, demonstrating that complex psychological constructs like impulsivity and its neurobiological orthogonal embodiment, behavioral response inhibition (BRI), can be effectively decomposed into measurable, neurobiologically-relevant components (deep endophenotypes). The successful discrimination of high versus low BIS-11 Factor I motor impulsivity groups across three distinct laboratory measures (models) confirmed the viability of deep endophenotyping approaches for advancing both theoretical understanding, and diagnostic and clinical translation.

Study Strengths and Limitations

Key strengths of this study include (a) the highly overpowered large, demographically representative sample ($n = 480$ for the main model, $n = 411$ for the refined model), which enabled discovery of an unexpected reaction time threshold for the GNG model, (b) a sophisticated analytical approach incorporating influence sensitivity analysis and cross-model convergent analysis, and (c) successful integration of multiple theoretical frameworks. The

study's comprehensive methodology, including three-tiered data validation and systematic outlier detection, enhanced confidence in the findings' robustness and generalizability. However, the cross-sectional design limited causal inferences, and the focus on BIS-11 Factor I motor impulsivity may not capture the full complexity of impulsivity (disinhibition) constructs.

Future Directions

The identified decomposed endophenotype candidates (theoretically and empirically selected features/deep endophenotypes) provide a foundation for developing neurocomputational AI models and digital twins of behavioral phenotypes, with a precisely defined input feature space regarding the most critical symptoms of many behavioral phenotypes (disinhibition/impulsivity) that maintain both empirical robustness and theoretical interpretability. Future research should validate these findings in independent samples and explore their utility in differential diagnosis, clinical assessment, and intervention targeting across diverse behavioral phenotypes, particularly ADHD, autism spectrum disorder (ASD), schizophrenia, and borderline personality disorder (BPD) populations represented in this study, with additional utility to other DSM behavioral phenotypes and neurological disorders, such as Parkinson's disease. Following reporting of the findings and description of a plurality of analysis, Chapter 5 will discuss interpretation and implications of these findings, recommendations for future research, and conclusions.

Chapter 5: Implications, Recommendations, and Conclusions

Introduction

The problem addressed by this study was that the endophenotype literature does not adequately characterize and segregate the dimensionality of the latent psychological constructs of impulsivity and impulse control (i.e., behavioral response inhibition [BRI]). The purpose of this quantitative quasi-experimental ex post facto study was to discriminate neurobiological and neuropsychological measures through assessing the relationships between subscales of the Barratt Impulsiveness Scale (BIS-11) for low and high trait motor impulsivity and subscales of three laboratory behavioral measures of BRI: the go/no-go task (GNG), the stop signal task (SST), and the Wisconsin card sorting test (WCST).

This study employed a quantitative quasi-experimental ex post facto design following the endophenotype hypothesis embedded Research Domain Criteria (RDoC) framework, utilizing one-way (one-factor) between subjects unpaired multivariate analysis of variance (MANOVA) to examine differences between extreme high and low BIS-11 Factor I motor impulsivity groups across three laboratory behavioral measures (models). Validated data for all three models were collected from 480 participants (upper and lower quartiles from 954 total valid tri-study completions) aged 18-40, representing both genders ($m = 284$, $f = 196$) and including substantial representation from four key self-reported behavioral phenotypes: attention deficit hyperactivity disorder (ADHD; ~20%), autism spectrum disorder (ASD; ~12%), schizophrenia (~4%), and borderline personality disorder (BPD; ~10%).

This study successfully identified four robust and one secondary (shadow) deep decomposed endophenotype via systematic analysis. Primary findings revealed significant multivariate effects for the WCST model, $p = .041$, partial $\eta^2 = .017$, driven by non-perseverative

errors (NPE), and the GNG model, $p = .005$, partial $\eta^2 = .026$, driven by commission errors (CE). A major methodological innovation—Cook's distance leverage-residual (influence) sensitivity analysis—substantially enhanced analytical precision by removing 69 influential cases (14.4% of the sample), revealing previously masked effects, including omission errors (OE) as significant predictors in both the GNG, $p = .012$, partial $\eta^2 = .016$, and SST, $p = .006$, partial $\eta^2 = .018$, models. Additionally, stop signal reaction time (SSRT) from the SST model emerged as a secondary candidate deep decomposed endophenotype, demonstrating initial significance, $p = .027$, but showing sensitivity to influential outliers in the refined analysis, $p = .054$, suggesting it warrants further validation in independent samples.

A Cross-Model Convergent Analysis identified Framework B (Model Representative; NPE + GNG_CE + SST_OE) as achieving the most optimal power-parsimony combination, partial $\eta^2 = .040$, among four statistically significant framework combinations, providing the optimal feature engineering for artificial intelligence (AI) applications while maintaining theoretical coherence and computational efficiency for neurocomputational digital twin AI applications. Figure 56 shows the contribution of each Framework B deep endophenotype to overall effect size, with commission errors from the go/no-go model representing the most significant contribution, the reaction time threshold optimization of speed and accuracy discovered in this study, and the pathway for clinical translation. Frameworks A, C and D were also statistically significant with Framework A (Optimal Performance; NPE, GNG_CE, GNG_OE, SST_OE, SSRT) achieving the largest effect size of all frameworks, partial $\eta^2 = .046$.

Figure 56
Framework B Deep Decomposed Endophenotypes: Component Effects, Integration, and Clinical Translation Pathway

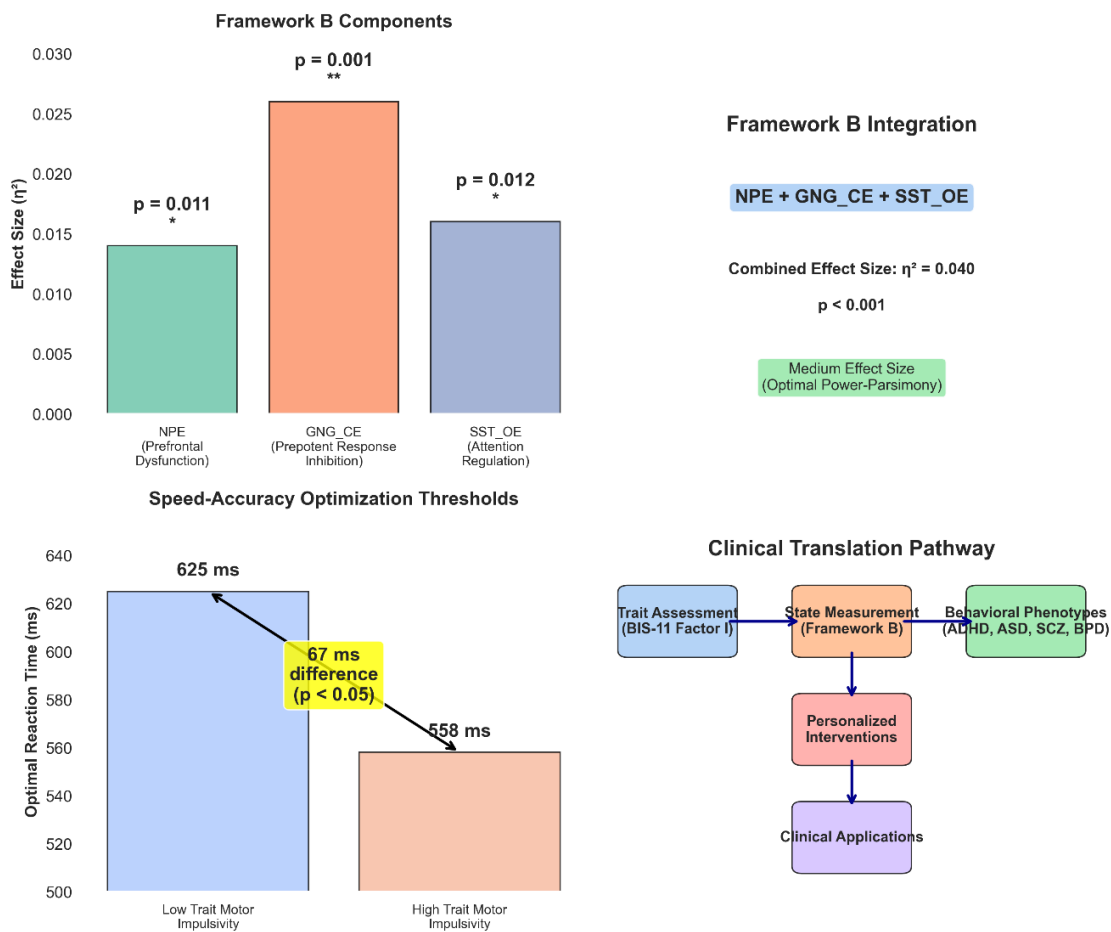
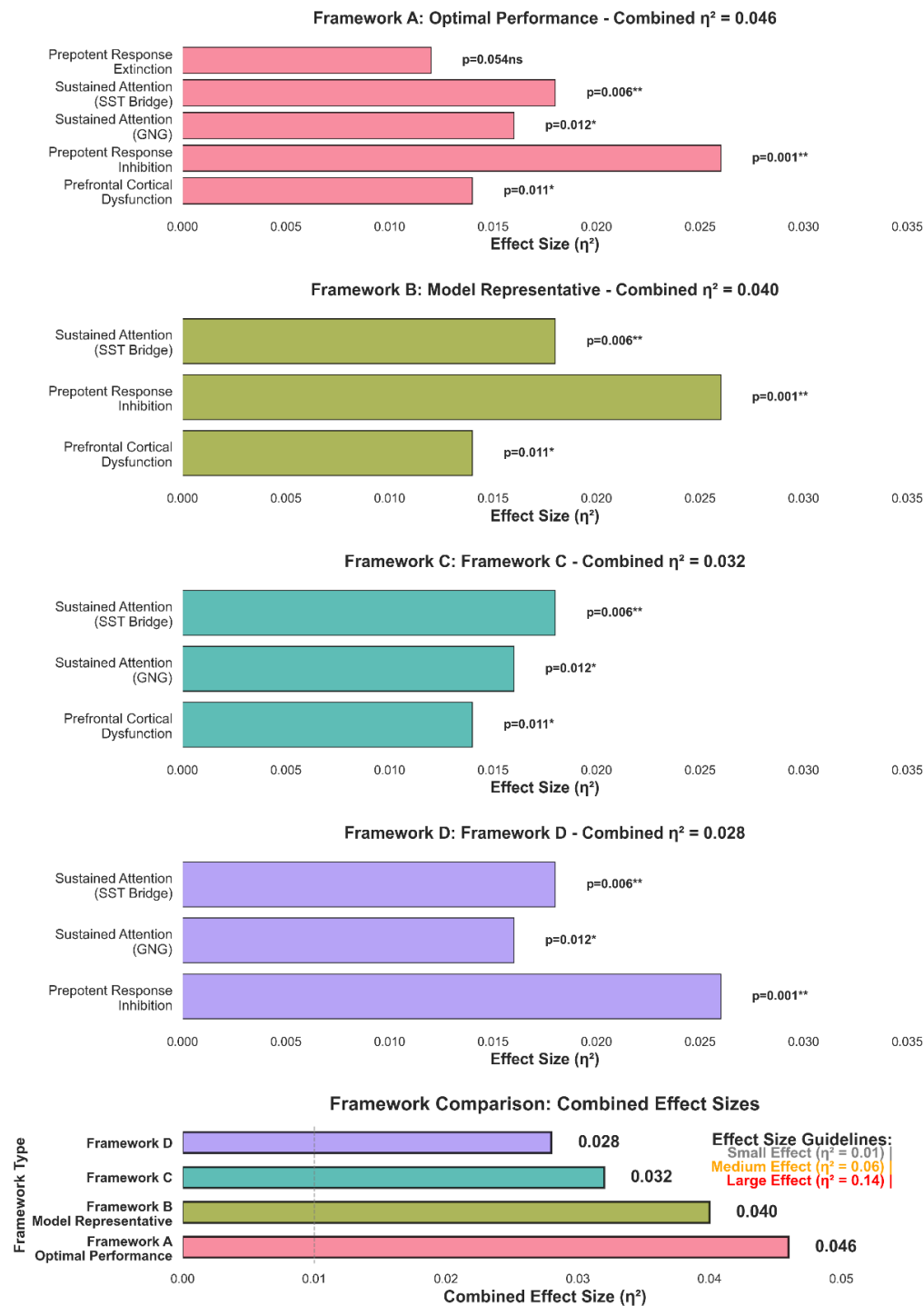


Figure 57 shows a comparison of all four frameworks showing a combination of p value and effect size contributions of each deep endophenotype to each framework where it achieved significance. At the bottom of the figure is a comparison of the effect sizes of each framework showing the power and parsimony advantages of the three deep endophenotype (feature) Framework B (Optimal Performance) and the pure power advantage of the five deep endophenotype (feature) Framework A (Model Representative).

Figure 57
Comparison of All Four Framework Combinations: Individual Deep Decomposed Endophenotypes and Combined Effect Sizes



Note: prepotent response extinction = SST_SSRT (stop signal reaction time for the SST model), sustained attention (SST bridge) = SST_OE (omission errors for the SST model), sustained attention (GNG bridge) = GNG_OE (omission errors for the GNG model), prepotent response inhibition = GNG_CE (commission errors for the GNG model), and prefrontal cortical dysfunction = WCST_NPE (non-preservative errors for the WCST model).

Overall, this study (a) arguably successfully solved the endophenotype characterization problem identified in the literature by decomposing behavioral response inhibition (BRI) into robust, measurable facets across multiple validated framework combinations, (b) successfully deployed Cook's distance leverage-residual (influence) sensitivity analysis as a potential new standard for behavioral neuroscience, and (c) successfully implemented a Cross-Model Convergence Analysis that identified empirically-validated feature sets for neurocomputational AI applications relating to trait motor impulsivity and state motor impulsivity's role in behavioral phenotypes.

Limitations of this study included a cross-sectional design limiting causal inferences, a focus on BIS-11 Factor I motor impulsivity, which may not capture the full complexity of impulsivity constructs, and reliance on self-reported diagnostic information for behavioral phenotype classification. Additionally, the substantial removal of influential cases through influence sensitivity analysis, while methodologically sound, may limit generalizability to populations with more extreme presentations.

Chapter Organization and Rationale

This chapter presents a comprehensive examination of the study's contributions organized into three distinct but complementary sections, each serving specific purposes in translating

empirical findings into theoretical understanding and practical applications. To address potential confusion regarding multiple discussions of future research, this organization deliberately distinguishes between different types and scopes of research recommendations.

The *Implications* section provides immediate theoretical and clinical significance of the findings, organized systematically by research question before integrating discoveries into comprehensive frameworks. This section examines how the validated deep decomposed endophenotypes resolve longstanding measurement problems, reconceptualize behavioral response inhibition theory, and enable new approaches to differential diagnosis. Clinical implications are integrated throughout specific methodological subheadings (e.g., Recommendations for Practice, Recommendations for Clinical Assessment Practice, Recommendations for Diagnostic Practice) to provide immediate guidance for translating empirical discoveries into clinical applications. Where this section includes *Future Research Directions* subsections, these represent immediate research questions that emerge directly from specific findings—targeted inquiries that could address particular theoretical gaps or validate specific mechanisms identified in the current study.

The major *Recommendations for Future Research* section presents comprehensive, systematic research programs designed to extend and validate the current findings through large-scale empirical investigation and advanced computational modeling. This section is organized into two complementary components: (a) empirical extensions that focus on traditional research methodologies, validation protocols, and systematic investigation approaches necessary to establish the deep endophenotypes as formal validated endophenotypes (intermediate phenotypes) meeting rigorous psychiatric genetics criteria, progressing through multi-modal validation studies and culminating in the Generic Model Study framework; and (b)

Neurocomputational Applications that address advanced neurocomputational artificial intelligence and digital twin modeling approaches leveraging the validated endophenotypes for next-generation research and clinical tools.

The distinction reflects different scholarly purposes: *Future Research Directions* within Implications identify specific theoretical questions and immediate research gaps that emerge from particular findings, while *Recommendations for Future Research* presents comprehensive research programs and systematic methodological frameworks for advancing the entire field. The Implications directions are targeted and theory-driven, while the Recommendations are programmatic and methodology-driven. This organization enables readers to engage with immediate theoretical questions while providing comprehensive roadmaps for both traditional empirical research and cutting-edge neurocomputational modeling approaches that together advance the field toward computational psychiatry RDoC invoked precision psychiatry and personalized intervention applications.

Through this comprehensive three-part examination, the study's contributions to endophenotype research, RDoC implementation, non-linear dynamical systems theory (NDST) applications, and translational computational neuroscience are synthesized to guide future scientific research and clinical applications across multiple levels of analysis and implementation complexity.

Implications

The findings of this study arguably have substantial theoretical, methodological, and clinical implications for understanding the dimensionality of impulsivity constructs, advancing behavioral response inhibition (BRI) research, identifying robust validated deep decomposed endophenotypes, better discriminating and differentiating behavioral phenotypes, and selection

of robust features for neurocomputational and digital twin AI models of behavioral phenotypes. The successful identification of robust deep decomposed endophenotypes arguably provides empirical validation for the Research Domain Criteria (RDoC) framework's premise that complex psychological constructs are best understood through their measurable component dimensions rather than as unitary phenomena. The following discussion examines the implications of each research question's (model's) findings and their collective contribution to addressing the identified problem of inadequate endophenotype characterization in the literature.

Key Findings and Discoveries

This study yielded at least six key discoveries that arguably fundamentally advance understanding of behavioral response inhibition (BRI) and trait-state impulsivity relationships: (a) the identification of Framework B (NPE + GNG_CE + SST_OE) from Chapter 4 as a robust three-component model arguably provides the first empirically validated power-parsimony optimized deep decomposed endophenotype combination for discriminating motor impulsivity groups, $p < .001$, partial $\eta^2 = .040$, representing a medium effect size; (b) the discovery of differential speed-accuracy optimization reaction time thresholds suggests that high trait motor impulsivity individuals perform optimally at significantly faster reaction times (558ms vs 625ms), challenging conventional *slow down* intervention approaches; (c) the reconceptualization of the GNG and SST tasks as measuring impulsivity versus compulsivity control mechanisms, respectively, may help resolve decades of measurement imprecision and discord in the literature; (d) the successful discrimination of motor impulsivity from choice impulsivity by the WCST through selective preservation of perseverative responses (PR), suggesting intact CN-dlPFC circuits while demonstrating motor impulsivity-specific prefrontal dysfunction through NPE; (e) the identification of hidden phenotypic heterogeneity within

control groups through bimodal distribution analysis, revealing a choice impulsivity subgroup among low motor impulsivity individuals, demonstrating that traditional control-treatment classifications may obscure important neurobiological complexity and validating multidimensional endophenotype profiling approaches; and (f) the successful resolution of the trait-state measurement discordance problem through methodological innovation demonstrates that endophenotype decomposition combined with extreme groups analysis can reveal genuine relationships that traditional correlational approaches systematically underestimate.

These six discoveries arguably make multi-modal contributions to the literature. They advance measurement precision (discoveries [c], [e], and [f]), theoretical understanding (discoveries [c], [d], and [e]), clinical applications (discoveries [b], [d], and [e]), and methodological innovation (discoveries [a], [d], [e], and [f]). Collectively, they provide the empirical foundation necessary for advancing multi-modal endophenotype research and developing next-generation assessment and interventions, neurocomputational AI models, and digital twins of behavioral phenotypes.

The following discussion examines these six discoveries through a structured analytical progression. First, implications for individual research questions establish the empirical foundation and methodological insights. Second, integrated analyses demonstrate how the findings of this study converge to resolve fundamental measurement problems in the field. Third, theoretical implications propose a reconceptualized framework for understanding BRI measurement targets. Fourth, neurobiological validation demonstrates how this theoretical framework aligns with established neural network circuit evidence. Fifth, the discussion examines how these theoretical and empirical advances enable future multi-modal research applications and clinical innovations. Further, the successful identification of Framework B deep

decomposed endophenotypes also directly resolves the core problem identified in Chapter 1 that "the endophenotype literature does not adequately characterize and segregate the dimensionality of the latent psychological constructs of impulsivity and impulse control." This study demonstrates that with proper methodological approaches, these constructs can be effectively characterized and segregated.

These six key discoveries provide the empirical foundation for examining their specific implications across individual research questions before integrating them into a comprehensive theoretical framework. The following analysis progresses systematically through each research question's contributions. This analysis establishes the methodological and theoretical advances that can potentially collectively transform the literature's understanding of behavioral response inhibition and trait-state impulsivity relationships.

Research Question 1: Implications of WCST Non-Perseverative Errors (NPE) as a Prefrontal Cortical Dysfunction Deep Decomposed Endophenotype

The identification of non-perseverative errors (NPE) as a robust deep decomposed endophenotype, $p = .011$, Cohen's $d = -0.234$, representing a small-to-medium effect size, has significant implications for understanding prefrontal cortical dysfunction deficits in motor impulsivity, with secondary implications for cognitive flexibility impairments. This finding directly addresses the present study's central problem by demonstrating that prefrontal cortical regulatory dysfunction, as measured through validated behavioral proxies, can be decomposed into specific, measurable components that reliably differentiate between high and low trait motor impulsivity groups. The robustness of this effect, confirmed through Cook's distance leverage-residual (influence) sensitivity analysis, $p = .016$, establishes NPE as a stable deep decomposed

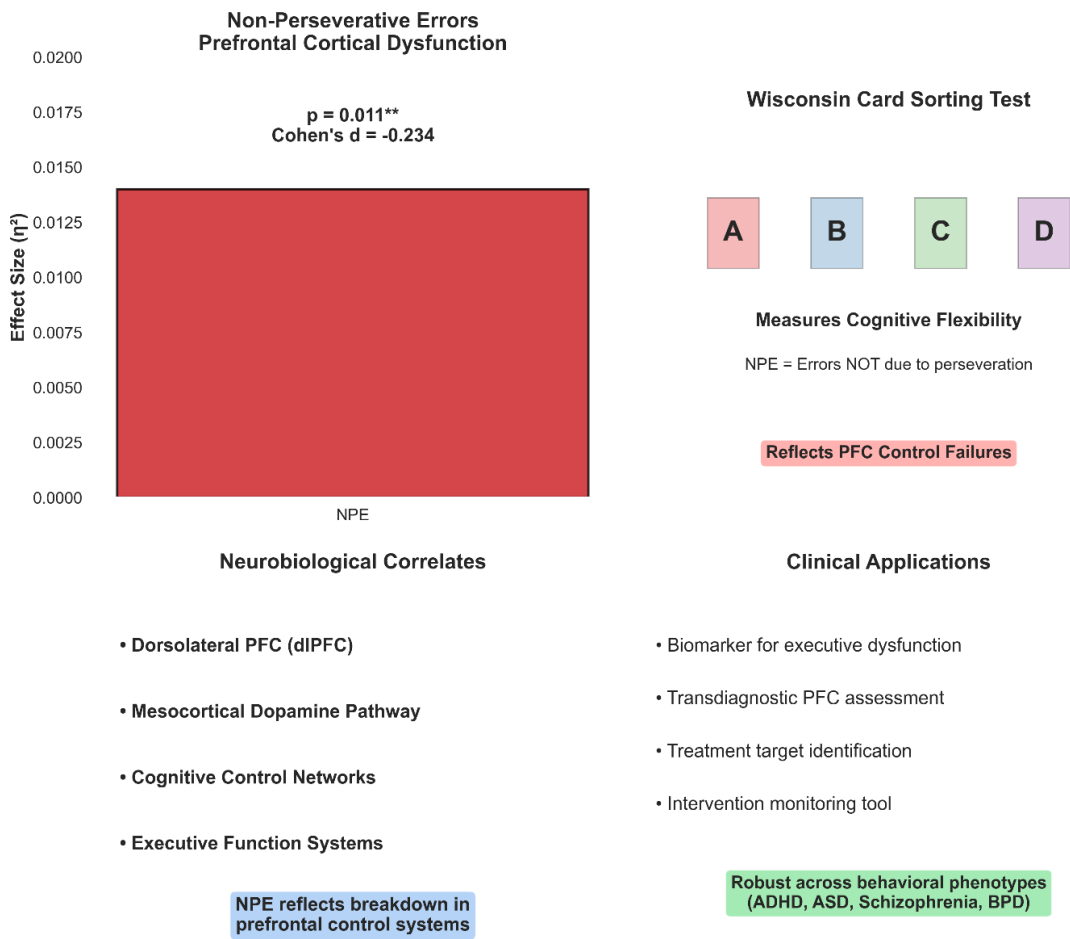
endophenotype for prefrontal cortical dysfunction and associated behavioral disinhibition characteristic of impulsive behavioral phenotypes.

These results extend Barkley's theory of inhibitory deficits by providing empirical evidence that behavioral response inhibition (BRI) deficits manifest through specific prefrontal cortical control failures rather than general executive dysfunction. As discussed in Chapter 2, the WCST serves as a validated proxy measure for frontostriatal circuit function, with NPE reflecting breakdowns in the integrated neural control systems, particularly the regulatory dysfunction that occurs when mesocortical dopaminergic circuits (VTA→dlPFC) fail and the system defaults to mesolimbic pathways (VTA→NAcc), disrupting the normal cortico-basal ganglia-thalamo-cortical loops that regulate behavioral responses and prevent impulsive responding (disinhibition).

This circuit-level framework, validated through neuroimaging studies detailed in Chapter 2 (Lombardi et al., 1999; Monchi et al., 2001; Waldthaler et al., 2022), suggests that NPE reflects distributed network dysfunction rather than solely focal prefrontal damage. The consistency of NPE effects across both original and refined analyses from Chapter 4 suggests that prefrontal cortical (PFC) dysfunction represents a fundamental neurobiological dimension underlying motor impulsivity that is resistant to measurement artifacts and individual differences in extreme responding. This stability has important implications for clinical assessment, as NPE could serve as a reliable neurobiologically-grounded endophenotypic marker for identifying individuals at risk for behavioral disinhibition and executive control impairments across multiple behavioral phenotypes. Figure 58 shows the significance of NPE as a deep endophenotype. While statistically significant, the effect size is small to moderate. The figure also shows NPE's marker level significance as both a neuropsychological deep endophenotype and neurobiological

deep endophenotype demonstrating the versatility of the WCST as both a neuropsychological measure and its role as a proxy for neurobiological etiology.

Figure 58
Non-Perseverative Errors as Prefrontal Cortical Dysfunction Deep Decomposed
Endophenotype: Neurobiological Correlates and Clinical Applications



The neurobiological implications of these findings are substantial, as NPE performance arguably serves as a validated proxy indicator of dorsolateral prefrontal cortex (dlPFC) regulatory function and its capacity to maintain cognitive control over behavioral responses, as established through the neuroimaging validation literature reviewed in Chapter 2. The findings of

this study suggest that BIS-11 Factor I trait motor impulsivity involves specific disruptions in prefrontal (PFC) cognitive control (including BRI) networks responsible for inhibiting prepotent responses and maintaining goal-directed behavior. Rather than simply representing cognitive flexibility deficits, elevated NPE appear to reflect failures in the prefrontal cortical systems that gate and regulate behavioral output, leading to the disinhibited response patterns characteristic of high trait motor impulsivity. This neurobiological specificity has important implications for differential diagnosis and targeted interventions deriving from those diagnosis, suggesting that treatments aimed at strengthening prefrontal cortical (PFC) function and enhancing behavioral control mechanisms may be particularly effective for individuals with high trait motor impulsivity profiles characterized by elevated NPE performance.

Factors that may have influenced the interpretation of these results include the relatively small effect size, partial $\eta^2 = .014$, indicating a small effect, which, while statistically significant and robust, suggests that prefrontal cortical (PFC) dysfunction represents but one component of a multifaceted motor impulsivity construct (and its orthogonal twin, behavioral response inhibition) involving distributed neural network systems. Additionally, the use of a computerized version of the WCST may have introduced task-specific variance that differs from traditional card-sorting RDoC laboratory behavioral measures, potentially affecting the sensitivity for detecting prefrontal cortical (PFC) dysfunction compared to alternative WCST implementations. The proxy nature of the WCST for prefrontal cortical (PFC), including orbitofrontal, function also means that other neural systems (neurobiological correlates) may contribute to NPE performance, requiring careful interpretation within the broader context of behavioral disinhibition mechanisms.

The neurobiological proxy nature of the WCST also extends to the caudate nucleus (CN). As noted in Chapter 2, (a) CN dysfunction is found in ADHD, ASD, and schizophrenia which also maps onto dopaminergic dynamics from D2/D3 receptors; (b) higher preservative responses (PR) on the WCST serve as a proxy for CN dysfunction (Lombardi et al., 1999; Monchi et al., 2001); (c) the relationship between WCST proxy invoked dlPFC and CN dysfunction in the above behavioral phenotypes implicates choice impulsivity (Antonelli et al., 2014; Martinez et al., 2020), (d) choice impulsivity is often more elevated in patients with, for example, ADHD and borderline personality disorder (Chan et al., 2023; Fineberg et al., 2014; Hamilton et al., 2016; Jung & Kim, 2023; Patros et al., 2016; Wang et al., 2020); (e) choice impulsivity and motor impulsivity are poorly correlated and even orthogonal (Hamilton et al., 2015; Wang et al., 2016); (f) dysfunction of projections via bypass of the mesocortical dopaminergic neural networks in favor of mesolimbic projections from the CN to the dlPFC implicates motor impulsivity; (g) dopamine transporter (DAT) tone in the CN has also been linked to both the GNG and SST (Dalley et al., 2011), and (h) consequently, studies, such as this study, that combine the BIS-11 with the WCST, GNG, and SST, can discriminate motor impulsivity and choice impulsivity, if one, but not the other is present.

As noted in Chapter 4, this study showed no significant difference between perseverative responses (PR) in the WCST model. Consequently, the absence of significant differences in PR between high and low BIS-11 FI-MI groups suggests that this study's sample did not exhibit the CN dysfunction typically associated with choice impulsivity. This finding implies that the high BIS-11 FI-MI treatment group's impulsivity profile is primarily characterized by motor impulsivity rather than choice impulsivity, supporting the orthogonal nature of these impulsivity subtypes documented in the literature (Hamilton et al., 2015; Wang et al., 2016). The

neurobiological implications are arguably significant: rather than reflecting CN-dlPFC dysfunction that would implicate mesocortical dopaminergic pathway deficits associated with choice impulsivity, the results suggest that motor impulsivity in this sample operates through alternative neural circuits. Specifically, the significant NPE findings indicate that motor impulsivity manifests primarily through prefrontal cortical dysfunction affecting cognitive flexibility and set-shifting abilities, while the intact PR performance suggests preserved CN-mediated executive control functions. This dissociation supports the theoretical framework that motor impulsivity may bypass mesocortical dopaminergic neural networks in favor of mesolimbic projections (as noted in point [f] above), without necessarily implicating the CN-dlPFC circuits that are characteristic of choice impulsivity. Therefore, this study's WCST findings provide evidence for motor impulsivity as a distinct endophenotype that can be discriminated from choice impulsivity through careful analysis of WCST performance patterns, particularly when PR remains intact while other executive control measures (NPE) show significant group differences.

The preservation of perseverative responses (PR) alongside elevated non-perseverative errors (NPE) arguably demonstrates what Chapter 2 described as "phenologs"—orthologous phenotypes that inform research across DSM behavioral phenotypes. The selective pattern of intact CN-dlPFC circuits (preserved PR) combined with motor impulsivity-specific prefrontal dysfunction (elevated NPE) validates the orthogonal relationship between motor and choice impulsivity constructs. This finding provides empirical support for the phenolog concept, where motor impulsivity and choice impulsivity represent measurable orthologous endophenotypes that can be systematically distinguished through neurobiological proxy measures, advancing

precision psychiatry applications through improved diagnostic differentiation across behavioral phenotypes.

The bimodal distribution pattern observed in the low motor impulsivity control group, as described in Chapter 4, provides additional validation for the orthogonal nature of impulsivity subtypes. The counterintuitive finding reported in Chapter 4 that low motor impulsivity individuals demonstrated greater perseverative response (PR) variability than high motor impulsivity individuals suggests the presence of a hidden choice impulsivity subgroup within the ostensible control group. As noted in Chapter 4's descriptive analysis, a subpopulation of control participants exhibited elevated perseverative responses (PR) while maintaining low BIS-11 Factor I motor impulsivity scores, indicating intact motor control alongside caudate nucleus (CN) dysfunction markers typically associated with choice impulsivity. This pattern supports the phenolog framework by demonstrating that traditional binary control-treatment classifications may obscure important neurobiological heterogeneity, arguably validating the need for multidimensional endophenotype profiling rather than unitary impulsivity conceptualizations. This finding strengthens the theoretical proposition that motor and choice impulsivity operate through distinct neural circuits, as these individuals showed preserved motor inhibition while exhibiting executive control dysfunction characteristic of choice impulsivity phenotypes.

Research Question 2: Implications of GNG Commission Errors (CE) and Reaction Time Threshold Discovery

The commission errors (CE) findings, $p = .001$, Cohen's $d = -0.297$, representing a small-to-medium effect size, provide compelling evidence for prepotent response inhibition as a core facet of motor impulsivity, validating central predictions of Barkley's theoretical framework. However, the most significant implication emerges from the novel speed-accuracy trade-off via a

reaction time threshold discovery. This novel discovery revealed that high trait motor impulsivity individuals achieve optimal inhibitory performance at faster reaction times (558ms) compared to low trait motor impulsivity individuals (625ms)—a 67-millisecond statistically significant difference with potentially profound theoretical and clinical implications.

This reaction time threshold (speed-accuracy optimization) finding fundamentally challenges putative conventional clinical wisdom that impulsive individuals universally benefit from *slowing down* interventions. Instead, this study's results suggest that motor impulsivity involves altered neural efficiency patterns where faster responding strategies are actually choice optimal for inhibitory control performance in individuals with behavioral response inhibition (BRI) deficits. This discovery may have significant implications for intervention design, indicating that treatment approaches should be individualized based on reaction time speed-accuracy optimization reaction time threshold profiles rather than applying uniform behavioral modification strategies across all impulsive presentations.

The emergence of omission errors (OE) as an additional significant predictor through influence sensitivity analysis, $p = .012$, Cohen's $d = -0.250$, representing a small to medium effect size, expands the theoretical understanding of prepotent response inhibition deficits to include sustained attention components. This dual-pathway model suggests that motor impulsivity affects both active inhibition processes (commission errors) and sustained attention maintenance (omission errors), providing a more comprehensive framework for understanding the multifaceted nature of behavioral response inhibitory deficits.

These findings have substantial implications for understanding the neurobiological mechanisms underlying impulsivity. The differential speed-accuracy optimization (reaction time threshold) patterns may reflect individual differences in neural processing efficiency within

attention and inhibition networks, suggesting that personalized neuroplasticity-based interventions could target specific optimization reaction time thresholds for maximum therapeutic benefit. These reaction time threshold patterns may reflect individual differences in the duration and efficiency of what Chapter 2 described as the *cognitive moment*—the temporal window that behavioral response inhibition (BRI) creates to "permit prefrontal cortical processing (i.e., executive functions) to evaluate the appropriateness of the response." High trait motor impulsivity individuals' optimization (reaction time threshold) at 558ms versus 625ms suggests that their cognitive moment operates optimally under compressed temporal constraints, challenging traditional assumptions about extending deliberation time for impulsive individuals. The co-occurrence of commission and omission error deficits implicates both conflict monitoring systems and sustained attention networks. This pattern points toward distributed neural dysfunction rather than localized deficits—specifically, dysfunction across multiple circuit-level systems rather than focal brain regions—suggesting that future research may benefit from EEG/ERP with eLORETA or fNIRS approaches that can capture the millisecond-level circuit dynamics and distributed system interactions necessary to validate these findings, as detailed in Chapter 2's comparative neuroimaging analysis.

These differential speed-accuracy optimization patterns may find neurobiological support in established ERP research on inhibitory control timing. As discussed in Chapter 2, the N2 ERP component appears between 200-270 milliseconds after no-go stimuli during successful prepotent response inhibition, reflecting conflict detection and initial inhibitory signaling in the anterior cingulate cortex. The approximately 288-358 millisecond temporal gap between N2 component offset (270ms) and the optimal reaction time thresholds identified in this study (558ms for high FI-MI, 625ms for low FI-MI) likely represents neural network integration time

required for inhibitory signals to propagate from conflict detection centers to motor control regions. This neurobiological framework suggests that high trait motor impulsivity individuals demonstrate more efficient neural-to-behavioral translation, achieving optimal inhibitory control through compressed neural processing pathways that align with their 558ms optimization threshold. The convergence of neurophysiological (N2 timing) and behavioral (reaction time threshold) endophenotypes provides empirical support for the RDoC multi-modal analysis approach, linking neural mechanisms directly to observable behavioral optimization patterns.

Methodological factors that may influence interpretation include the specific parameters used in the GNG task ($pNoGo = .2$, 1,500ms trial duration), which may have created optimal conditions for detecting speed-accuracy reaction time trade-offs that might not emerge under different timing constraints. Additionally, the quadratic relationship between mean reaction time (mRt) and commission errors (CE) suggests nonlinear (NDST informed) optimization functions that may require more sophisticated modeling approaches in future research.

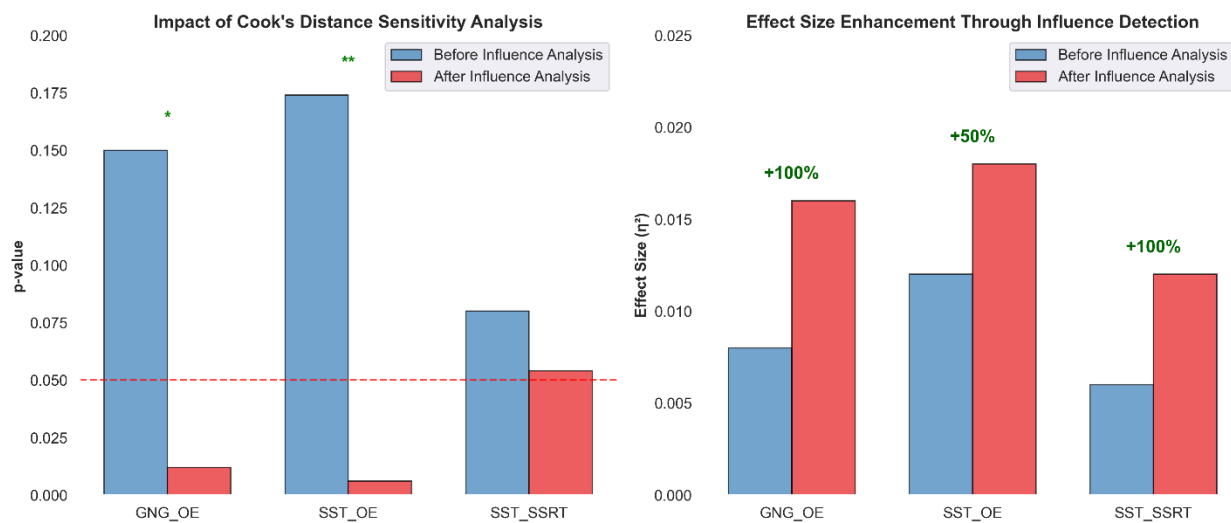
Research Question 3: Implications of SST Findings and Transdiagnostic Attention Deficits

The Stop Signal Task (SST) model findings provide complex but theoretically important implications for understanding prepotent response extinction and sustained attention deficits in trait motor impulsivity. While the original primary multivariate (MANOVA) analysis yielded non-significant effects, $p = .174$, the substantial signal recovery achieved through Cook's distance leverage-residual sensitivity analysis, $p = .019$, demonstrates the critical importance of addressing influential outliers in behavioral neuroscience research. This methodological insight has broad implications for the field, suggesting that traditional analytical approaches may systematically underestimate effect sizes and miss genuine group differences due to extreme response patterns. Figure 59 shows the impact of Cook's distance leverage-residual (influence)

sensitivity analysis on both p -value and effect size. The influence analysis yielded substantial improvement in both significance and effect size.

Figure 59

Impact of Cook's Distance Leverage-Residual Sensitivity Analysis on Effect Detection and Statistical Power



The latent emergence of omission errors (OE) as a highly significant predictor, $p = .006$, Cohen's $d = -0.271$, representing a small-to-medium effect size, following influence sensitivity analysis has profound implications for understanding the transdiagnostic nature of attention deficits in the context of behavioral response inhibition across behavioral phenotypes. The parallel OE effects observed in both GNG and SST models suggest that sustained attention deficits represent a core feature of trait motor impulsivity that transcends specific task demands or measurement contexts. This consistency supports the concept of attention regulation as a fundamental dimension underlying multiple psychiatric presentations, aligning with RDoC's

dimensional approach to understanding shared cognitive vulnerabilities across diagnostic categories.

The borderline significance of stop signal reaction time (SSRT) following influence sensitivity analysis, $p = .054$, provides important insights into the complexity of prepotent response extinction mechanisms. While, as discussed in Chapters 2 and 3, SSRT represents a theoretically critical measure of inhibitory control capacity, its sensitivity to influential outliers suggests that individual differences in stopping ability may be more variable than previously assumed. This variability has important implications for clinical assessment, indicating that SSRT interpretation should consider individual response patterns and may require multiple measurement occasions for reliable characterization.

The transdiagnostic implications of sustained attention deficits are particularly significant given the high comorbidity rates observed in this study (55.4% ADHD-ASD overlap, 43% BPD-schizophrenia overlap). The consistent OE effects across multiple laboratory behavioral task measures suggest that attention regulation difficulties may represent a shared risk factor or maintaining mechanism across diverse behavioral phenotypes, supporting dimensional rather than categorical approaches to psychopathology classification.

Factors influencing interpretation of SST results include the complexity of the race model assumptions underlying the SSRT calculation, which may be violated in populations with highly variable response patterns. Additionally, the substantial improvements in data quality following influential outlier removal (50% variance reductions in some measures) suggest that extreme response patterns may reflect qualitatively different cognitive strategies rather than quantitative variations along a single dimension. Finally, preliminary pilot testing of the SST model with live test participants demonstrated frustration with the pilot sample in that the regression-towards the

mean approach discussed in Chapter 3 meant that the task punished, rather than rewarded, success, which may have consequently exacerbated impulsive response dynamics in the study group, particularly the upper quartile of the study group. Having examined the individual implications of each research question, the discussion now turns to how these findings converge to address the study's central objectives and broader theoretical frameworks.

Having examined the individual contributions of each research question, the analysis now turns to how these findings converge to address the study's central objectives and broader theoretical frameworks. The integration of WCST prefrontal cortical dysfunction markers, GNG prepotent response inhibition patterns, and SST attention regulation mechanisms reveals emergent properties that exceed the sum of their individual contributions (recall the NDST discussion from Chapter 2), providing the comprehensive endophenotype framework necessary for advancing both theoretical understanding and practical applications.

Integrated Implications Across Research Questions

The success of the decomposition approach in revealing genuine trait-state relationships addresses the definitional complexity of BRI (and impulsivity) noted in Chapter 2, where "a plurality of definitions" exists in the literature. By focusing on specific behavioral components rather than global BRI constructs, this study demonstrates that "affirmative inaction or interruption of an action in favor of cognitive processing" can be meaningfully measured and related to trait motor impulsivity when appropriate methodological precision is applied. Further, the collective findings across all three research questions (models) provide compelling evidence for the successful decomposition of behavioral response inhibition (BRI) into distinct, measurable facets that differentially associate with motor impulsivity. This achievement directly addresses the fundamental problem identified in the literature—inadequate characterization and

segregation of impulsivity construct dimensionality—while providing empirical validation for the RDoC framework's approach to psychiatric classification.

The identification of Framework B (NPE + GNG_CE + SST_OE) as an optimal feature combination represents a significant advancement for both theoretical understanding and practical applications. This three-component model captures complementary aspects of executive dysfunction (cognitive flexibility, prepotent response inhibition, and sustained attention) while maintaining statistical robustness and theoretical coherence. The strong multivariate effects, $p < .001$, partial $\eta^2 = .040$, representing a medium effect size, achieved by this combination exceed those of individual models, demonstrating the value of integrated assessment approaches for capturing the multifaceted nature of impulsivity constructs.

Further, the methodological implications of Cook's distance leverage-residual (influence) sensitivity analysis extend far beyond this specific study, providing a framework for enhancing analytical precision in behavioral neuroscience research. The revelation of previously masked effects (GNG_OE, SST_OE) through influence detection demonstrates that traditional analytical approaches may systematically underestimate the complexity of cognitive-behavioral relationships. This insight has important implications for reinterpreting existing literature and designing future studies with enhanced sensitivity to genuine but previously undetected effects.

The broader implications for understanding behavioral phenotype comorbidity are arguably substantial. The successful identification of transdiagnostic attention deficits (OE effects) provides a mechanistic explanation for the high comorbidity observed between ADHD, ASD, schizophrenia, and BPD in this sample. Rather than viewing comorbidity as diagnostic confusion, imprecision, or measurement error, these findings suggest that shared cognitive vulnerabilities may represent common pathways to diverse phenotypic presentations, supporting

the development of mechanism-based rather than symptom-based intervention approaches. Collectively, these integrated findings demonstrate that endophenotype decomposition combined with methodological innovation can resolve longstanding measurement problems while providing the foundation for advancing both theoretical understanding and clinical applications.

Trait-State Impulsivity Integration: Resolving the Measurement Discordance Problem

The findings of this study provide crucial insights into the long-standing problem of weak associations between self-report measures of trait impulsivity and laboratory behavioral measures of state impulsivity discussed in detail in Chapter 2, directly addressing the measurement discordance identified by Aichert et al. (2012) who found that BIS-11 trait impulsivity explained only 12% of the variance in laboratory behavioral measures of prepotent response inhibition. The contrast between Aichert et al.'s 12% variance explained and the current study's robust group discriminations highlights how the methodological approach fundamentally influences trait-state impulsivity relationship detection. The success of endophenotype decomposition and extreme groups (1st and 3rd quartiles rather than 50% quantiles) analysis in revealing relationships that traditional correlational methods may underestimate, suggests that the weak correlation problem may reflect methodological limitations rather than a fundamental problem with construct validity.

The endophenotype decomposition approach employed in this study—parsing both trait impulsivity (BIS-11 Factor I trait motor impulsivity) and laboratory behavioral measures (state impulsivity) into specific facets and components—validates the theoretical proposition advanced in Chapter 2 that stronger relationships would emerge when laboratory behavioral measures are "dimensionalized and decomposed into their factors, facets, components, and features." The identification of Framework B (NPE + GNG_CE + SST_OE) as robust discriminators of high

versus low BIS-11 Factor I trait motor impulsivity groups demonstrates that facet-specific analysis can reveal genuine trait-state correspondences that global correlational approaches systematically underestimate. The success of deep decomposed endophenotypes also validates the Chapter 1 proposition that "subscales of self-report measures are better correlated with subscales of behavioral measures than higher order scales are," arguably providing the first empirical demonstration of this theoretical prediction.

Motor Impulsivity as the Operational Bridge Between Trait and State Impulsivity.

The findings of this study support the theoretical framework established in Chapter 2 that motor impulsivity serves as the "operational symptomatic embodiment" of trait impulsivity, functioning as the observable form of impulsivity that can be a product of other, latent forms of impulsivity, such as choice impulsivity and cognitive impulsivity. As conceptualized in Chapter 2, motor impulsivity represents "an act, a motor action" that manifests as observable behavioral disinhibition in laboratory behavioral contexts. The robust effects observed across multiple behavioral response inhibition (BRI) facets suggest that BIS-11 Factor I trait motor impulsivity captures the trait-level vulnerability that translates into state-level behavioral disinhibition when cognitive control systems are challenged (what mathematically amounts to a perturbation problem, a phase shift inflection from an NDST perspective).

The identification of robust effects for both GNG (prepotent response inhibition) commission errors (CE) and borderline effects for SST (prepotent response extinction) provides empirical support for the direct mapping of these laboratory behavioral measures onto Barkley's first two facets of behavioral response inhibition (BRI) established in Chapter 2, while the emergence of omission errors (OE) across both tasks raises important questions about the role of Barkley's third facet (interference control) in motor impulsivity presentations. This finding may

have profound implications for understanding how stable personality traits (trait impulsivity) manifest as dynamic behavioral responses (state impulsivity) under specific task demands.

The WCST findings provide additional support for the orthogonal relationship between motor and choice impulsivity by demonstrating that high motor impulsivity individuals show preserved caudate nucleus (CN) function (intact PR) while exhibiting prefrontal cortical dysfunction (elevated NPE). This selective preservation pattern arguably validates the phenolog concept from Chapter 2, where motor impulsivity and choice impulsivity represent "orthologous phenotypes" that can be empirically distinguished through neurobiological proxy measures, supporting dimensional rather than unitary conceptualizations of impulsivity constructs.

The discovery of a choice impulsivity subgroup within the low motor impulsivity control group, as reported in Chapter 4's bimodal distribution analysis, provides empirical evidence for the complex phenotypic landscape underlying impulsivity constructs. This mixed phenotype discovery demonstrates that individuals can exhibit choice impulsivity (elevated PR indicating CN dysfunction) without motor impulsivity (low BIS-11 Factor I scores), supporting the orthogonal relationship between these impulsivity facets documented in the literature. The bimodal distribution pattern suggests that future endophenotype research should assess multiple impulsivity dimensions simultaneously to identify pure motor impulsivity profiles, pure choice impulsivity profiles, mixed presentations, and true low impulsivity controls, advancing precision psychiatry through improved phenotypic stratification.

Reaction Time Threshold Discovery Implications and Recommendations for Practice. Further, the identification of differential speed-accuracy optimization reaction time threshold patterns provides novel insights into the temporal dynamics of trait-state relationships. High trait motor impulsivity individuals' achievement of optimal performance at statistically

significant faster reaction times (558ms versus 625ms) suggests that trait-level neural efficiency differences influence state-level performance optimization strategies. This discovery bridges the temporal stability characteristic of trait impulsivity with the dynamic, environmentally-sensitive nature of state impulsivity by suggesting that stable individual differences in behavioral processing efficiency, which may reflect underlying neural circuit function as established through the proxy framework detailed in Chapter 2, determine optimal perturbational behavioral response patterns in laboratory behavioral contexts.

For example, across the four behavioral phenotypes examined in this study (ADHD, ASD, schizophrenia, BPD), individuals scoring in the high Factor I trait motor impulsivity range may require interventional approaches that, counterintuitively, capitalize on their faster neural processing optimization rather than on conventional strategies discussed in Chapter 2 designed for slower processing speeds. This suggests that treatment protocols should be personalized based on speed-accuracy reaction time optimization (threshold) profiles rather than on applying uniform pacing across diagnostic categories.

As one example, individuals with borderline personality disorder (BPD), $n = \sim 23$ (based on percentage in the full study sample of $n = 954$), 4.8%, who demonstrated elevated Factor I trait motor impulsivity scores, $\bar{x} = 18$, 77th percentile, in this study, may experience optimal emotional regulation not through traditional *pause and reflect* strategies, but through faster cognitive processing approaches that align with their 558 ms optimization reaction time threshold. This finding challenges conventional dialectical behavior therapy (DBT) assumptions, for example (see Chapter 2), about slowing down emotional responses and suggests that BPD individuals may benefit from behavioral interventions that harness their faster processing

capabilities rather than attempting to override them, which also may call into question psychopharmacological interventions typically used.

Similarly, individuals with ADHD, $n = \sim 101$, 21%, who demonstrated elevated BIS-11 Factor I trait motor impulsivity scores, $\bar{x} = 17$, 75th percentile, and comprised the largest behavioral phenotype group in this study, may achieve optimal cognitive control (using an RDoC domain) through faster-paced behavioral interventions rather than traditional approaches that emphasize behavioral slowing, which, again, may call into question standard of care psychopharmacological interventions discussed in Chapter 2. This optimization pattern provides a neurobiological rationale for why many ADHD individuals report improved focus and performance in high-stimulation environments that would overwhelm individuals with lower motor impulsivity traits.

In educational behavioral intervention settings, the reaction time threshold discovery of this study may suggest that *extra-time*, *pull-out*, and *quiet time* accommodations often provided under individualized education plans (IEPs) and so called 504-plans for children with impulse control disorders (particularly ADHD and ASD) may potentially counterintuitively undermine optimal performance strategies for such children. It should be noted, however, that there is no overlap between the sample for this study and a population of ages under 18. As noted in Chapter 3, lifespan development of prefrontal cortical (PFC) processing and executive function capabilities develops along different temporal scales. In all these cases is an inherent suggestion that interventions may be better designed to adapt to the patient (or the student), rather than forcing the patient to adapt to neurotypical behavioral dynamics.

The optimization reaction time threshold findings have important developmental implications aligned with Chapter 2's framework that endophenotypes should serve as "early

predictors or primordial diagnostic markers in healthy pre-symptomatic and prodromal individuals." The statistically significant 558ms vs 625ms optimization difference may represent stable neural efficiency patterns that could be detected before full symptom emergence, providing the "phylogenetically more primitive" markers described in Chapter 2 that are necessary for early intervention approaches. Building on the resolution of trait-state measurement discordance, these findings support a fundamental reconceptualization of how BRI tasks should be understood and applied.

The neurobiological plausibility of these reaction time threshold patterns receives additional support from the temporal convergence with established ERP endophenotypes. The sequential processing model—from N2 conflict detection (200-270ms) through neural network integration (270-558ms) to behavioral optimization (558ms)—provides a mechanistic framework for understanding how stable trait differences in neural efficiency manifest as dynamic behavioral adaptations. This temporal convergence arguably validates the deep endophenotyping approach by demonstrating measurable correspondence between neurophysiological markers established in Chapter 2 and the novel behavioral thresholds identified in this study, supporting the proposition that true endophenotypes should bridge multiple levels of analysis from neural circuits to behavioral phenotypes.

Theoretical Implications: Reconceptualizing BRI Measurement Targets

The findings of this study suggest a fundamental reconceptualization of what the GNG and SST laboratory behavioral measures actually measure within the BRI framework. While both tasks have traditionally been characterized as measuring behavioral response inhibition (BRI) generally, the findings of this study support a more nuanced theoretical model where GNG primarily measures impulsivity control mechanisms while SST primarily measures compulsivity

control mechanisms, both operating through distinct BRI facets as outlined in Chapter 2. For example, as described in Chapter 3 in light of the discussion of impulsivity versus compulsivity in Chapter 2, deficits in SSRT in the SST have been more significant in obsessive compulsive disorder (OCD) than in ADHD, ASD, or schizophrenia (Lipszyc & Schachar, 2010) supporting the above role as a “potential measure of latent compulsivity and preservation.”

This reconceptualization may help resolve several conflicting findings in the literature, most notably the Sanchez-Kuhn et al. (2017) study discussed in Chapter 2, which, contrary to those authors' hypothesis, found virtually no relationship between BIS-11 impulsivity scores and GNG performance (most notably between CE and Factor II motor impulsivity [which combines Factor I motor and attentional impulsivity]) but did find a relationship between GNG and the MOCI compulsivity measure. This study's framework, however, suggests this paradox reflects methodological limitations and differences rather than construct validity issues:

First, Sanchez-Kuhn et al. (2017) used total BIS-11 scores rather than Factor I motor impulsivity subscale scores. The divergent findings reveal a critical measurement issue: (a) while the present study demonstrated that high Factor I trait motor impulsivity reliably predicts more commission errors (CE), Sanchez-Kuhn's high CE group showed no differences on Factor II motor impulsiveness. Logically, if commission errors (CE) reflect motor impulsivity, high CE groups should demonstrate higher motor impulsivity scores. This apparent contradiction suggests that Factor II's combination of motor and attentional impulsivity Factor I subscales may dilute the true motor impulsivity effects. High CE individuals likely possess elevated motor impulsivity (driving their commission errors) but may simultaneously exhibit lower attentional impulsivity. When these opposing factors are combined into Factor II, they may effectively cancel each other out, resulting in no observable group differences despite genuine underlying motor impulsivity

variations. This pattern demonstrates how composite scores (essentially dimensional reduction techniques) can obscure true relationships that decomposed (dimensionalisation techniques) measurements reveal, with Factor I motor impulsivity (pure-dimensionalized) detecting effects that Factor II motor impulsiveness (composite-dimensionally reduced) systematically masks.

Second, the authors used a different version of the GNG than used for this study with different stimuli and presentation. In addition, parameter settings differed between Sanchez-Kuhn et al., (2017) and the present study, which followed the optimization suggestions of Wessel (2017) and Deng et al. (2023). For example, pNoGo of .25 for Sanchez-Kunh et al. (2017) vs. .2 for this study and pGo of .75 vs. .8, 206 trials vs. 250 trials, fixation duration of 500 ms vs. 400 ms, and exclusion of data with a CE rate greater than .8 or OE rate of greater than .5, exclusion criteria that Sanchez-Kuhn et al. (2017) did not implement. These differences may have materially contributed to the apparently contradictory results between Sanchez-Kunh et al. (2017) and the present study and further highlight the GNG task's lack of convergent validity noted in Chapter 3 by Langenecker et al. (2007) due to variety in types of stimuli and measurement parameters including pGo and pNoGo signals, and time delay of signal and separation of stimuli discussed.

Third, while Sanchez-Kunh et al. (2017) used an extreme groups methodology, their study groups comprised low commission errors (CE) and high CE groups from GNG scores rather than any bifurcation of BIS-11 scores. The high CE group had significantly higher compulsivity levels than the low CE group (Sanchez-Kunh et al., 2017). However, while the high CE group had significantly higher compulsivity levels (MOCI scores) than the low CE group, the two groups did not significantly differ on Factor II motor impulsiveness BIS-11 subscale scores—the very measure that should have differentiated them if commission errors (CE)

reflected motor impulsivity rather than compulsivity (but see above the masking effects of Factor II over Factor I). Finally, Sanchez-Kunh et al. (2017) also did not conduct influence sensitivity analysis that revealed the robust GNG-impulsivity relationship in the current study, again potentially masking significant effects with extreme influential outliers.

These findings provide compelling evidence that multidimensional constructs require decomposition (dimensionalization) to reveal genuine mechanisms that composite measures systematically obscure. Consequently, the fact that Sanchez-Kuhn et al. found GNG-compulsivity relationships suggests that behavioral control measures may show cross-construct associations when impulsivity-specific effects are masked by methodological constraints, further supporting the need for the endophenotype decomposition approach employed in this study. These substantial methodological differences likely explain the divergent findings, as GNG task performance is highly sensitive to stimulus (perturbational) parameters and analytical approaches.

The GNG-Impulsivity Connection. The robust discrimination of motor impulsivity groups through GNG commission errors (CE), $p = .001$, Cohen's $d = -0.297$, supports the proposition that the go/no-go (GNG) task primarily measures prepotent response inhibition (Barkley's Facet 1), which aligns with impulsivity's characteristic pattern of "reward-driven" and "risk-seeking" behavior described in Chapter 2. The GNG paradigm captures the fundamental impulsivity challenge: stopping before you start—the ability to inhibit a primed prepotent response before execution. High trait motor impulsivity individuals' failure to inhibit prepotent responses in the GNG task reflects the core impulsivity deficit of acting without forethought.

The SST-Compulsivity Connection and Impulsivity-Compulsivity Bridge.

Conversely, the more complex SST findings—requiring influence sensitivity analysis to reveal effects and showing borderline significance for SSRT—suggest that the stop signal task primarily measures prepotent response extinction (Barkley's Facet 2), which aligns with compulsivity's characteristic "relief-driven" and "harm-avoiding" patterns described in Chapter 2. However, the SST's methodological complexity may also reflect its unique position as a bridge between impulsivity and compulsivity constructs. The SST paradigm captures the fundamental compulsivity challenge: stopping after you've started—the ability to extinguish an ongoing response that has become maladaptive. This maps directly onto compulsivity's defining feature of *behavioral stickiness* with abnormal perseveration on actions that are often maladaptive. Simultaneously, the *stopping after starting* mechanism is equally relevant to impulsivity, where individuals must learn to terminate impulsive actions once initiated. This dual relevance may explain why SST effects required sophisticated analytical approaches to detect, as the task may be measuring the intersection where impulsivity and compulsivity "merge at deficits in behavioral response inhibition" as noted in Chapter 2. The SST thus represents not just a compulsivity measure, but potentially, the critical bridge mechanism through which impulsive tendencies can transition into compulsive patterns (e.g., hyper fixation, and thus perseverant, by ADHD behavioral phenotypes following rewarded impulsive actions), providing a neurobiological pathway for understanding how these orthogonal yet correlational constructs interact in clinical presentations.

Neurobiological Implications. This reconceptualization suggests that impulsivity and compulsivity, while "orthogonal yet arguably correlational" as noted in Chapter 2, converge at BRI deficits through distinct neural pathways. The differential reaction time threshold

optimization patterns observed in the GNG task (558ms vs 625ms thresholds) demonstrate that impulsivity control mechanisms operate optimally under compressed time constraints. This finding aligns with the distinct neural circuit patterns described in Chapter 2, where impulsivity control may primarily engage mesocortical dopaminergic pathways (VTA→PFC) optimized for rapid executive decision-making. The statistically significant 67-millisecond optimization difference observed in this study may reflect the temporal signatures of these impulsivity-specific neural network circuit operations.

While this study's SST findings do not identify comparable reaction time optimization data for compulsivity mechanisms, the theoretical framework predicts that compulsivity control may require extended processing time for prepotent response extinction, potentially engaging mesolimbic pathways (VTA→NAcc) with different temporal dynamics. The integration of GNG (impulsivity-optimized) and SST (compulsivity-relevant) findings in Framework B suggests that effective behavioral control requires coordination between these temporally distinct neural systems, with impulsivity control providing rapid initial inhibition and compulsivity control managing sustained prepotent response extinction. Future research examining SST-SSRT optimization patterns could test whether compulsivity mechanisms indeed operate optimally at longer temporal thresholds, completing the temporal dynamics picture of these orthogonal yet interactive control systems.

Clinical Assessment Implications and Recommendations for Clinical Assessment Practice

This framework arguably has profound implications for differential diagnosis and treatment planning. Framework B components (NPE + GNG_CE + SST_OE) and potentially Frameworks A, C, and D may provide comprehensive assessment batteries that capture multiple dimensions of cognitive control (invoking an RDoC domain) deficits. GNG_CE reflects pure

impulsivity control deficits (Factor I trait motor impulsivity), while SST_OE may represent the critical bridging mechanism between impulsivity and compulsivity through attentional regulation failures. This interpretation aligns with the transdiagnostic emergence of omission errors (OE) across both GNG and SST models, suggesting that sustained attention deficits (Factor I attention and Factor II attentional impulsiveness) serve as the pathway through which impulsivity vulnerabilities can manifest as compulsive-like perseverative patterns.

The borderline significance of SSRT, $p = .054$, supports this framework by suggesting that while pure motor impulsivity effects (Factor I trait motor impulsivity) do influence prepotent response extinction, the stronger SST_OE effects indicate that attentional regulation failures may be the primary mechanism through which trait motor impulsivity translates into *stopping after starting* difficulties. This dual-pathway model suggests that SST_OE captures the attentional bridge between impulsivity and compulsivity, while SSRT reflects residual motor impulsivity influences on prepotent response extinction mechanisms.

NPE serves as a general executive and prefrontal cortical dysfunction candidate deep endophenotype. The high comorbidity rates observed in this study (e.g., 55.4% ADHD-ASD overlap) may reflect individuals with deficits in both pure motor control (GNG_CE) and attentional bridge mechanisms (SST_OE), requiring integrated treatment approaches that address the full spectrum from impulsivity through attentional regulation to compulsive-like perseveration.

Behavioral Phenotype-Specific Framework Applications. The current study's findings have distinct implications for understanding how Framework B (and potentially Frameworks A, C, and D) apply across the four behavioral phenotypes examined in this study (as well as other behavioral phenotypes where impulsivity plays a material role, and also neurological conditions,

such as Parkinson's disease), each presenting unique impulsivity profiles that may require tailored endophenotype approaches.

ADHD-Specific Framework Applications. ADHD, identified as the "poster child of impulsivity" in Chapter 2, may show optimal discrimination through Framework B given its arguably pure motor impulsivity focus. The three ADHD subtypes described in Chapter 2 may require different framework optimization: predominantly inattentive type may favor frameworks emphasizing attention regulation (potentially Framework C or D), while hyperactive-impulsive and combined types may show strongest Framework B discrimination. The 558 ms reaction time optimization finding is particularly relevant for ADHD interventions, challenging traditional *slow down* approaches and supporting high-stimulation cognitive training programs that capitalize on faster processing optimization. ADHD's frontoparietal and frontostriatal circuit dysfunction described in Chapter 2 aligns with Framework B's NPE (prefrontal cortical dysfunction) and GNG_CE (motor inhibition) components. The current findings suggest that ADHD individuals may require interventions that work with, rather than against, their faster neural processing optimization patterns.

ASD-Specific Framework Applications. ASD presents a unique profile where impulsivity emerges through executive dysfunction rather than primary motor impulsivity, with significant compulsivity overlap through "restricted, repetitive patterns of behavior" described in Chapter 2. This positions ASD as critical for validating the SST as an impulsivity-compulsivity bridge, where SST_OE may capture the attention regulation failures that underlie both repetitive behaviors and task-switching difficulties described in Chapter 2. The three ASD severity levels may show different framework patterns: Level 1 (high-functioning Aspergers type) individuals may show selective SST_OE elevations reflecting cognitive inflexibility, while Level 3

presentations may require alternative frameworks given severe communication limitations. ASD's ACC-mPFC and insula dysfunction described in Chapter 2 suggests potential overlap with schizophrenia patterns but with different severity profiles. The "cannot inhibit their own perspective" cognitive impulsivity pattern described in Chapter 2 may specifically map onto attention regulation failures captured by SST_OE.

Schizophrenia-Specific Framework Applications. Schizophrenia, described as showing "BRI deficits as bad or worse as those with impulse control disorders" in Chapter 2, may require framework combinations beyond Framework B given the severity of symptomatic presentation. The dopamine hypothesis centrality described in Chapter 2 directly validates the mesocortical/mesolimbic circuit predictions underlying Framework B discrimination. Different symptom clusters may associate with different frameworks: positive symptoms (delusions, hallucinations) may correlate with NPE elevations reflecting prefrontal deterioration, while negative symptoms may show different patterns reflecting the "six A's" (alogia, affective flattening, anhedonia, asociality, avolition, apathy) described in Chapter 2. The diagnostic flexibility allowing varied symptom combinations suggests that framework selection may need to be symptom-cluster specific rather than diagnosis-specific. Given that schizophrenia represents the most severe impulsivity presentation among the four behavioral phenotypes described in detail in this study, Framework B components may show ceiling effects, necessitating alternative frameworks or supplementary measures.

BPD-Specific Framework Applications and BPD-Schizophrenia Differential Diagnosis. As suggested in Chapter 2, BPD arguably presents the most complex impulsivity profile. BPD has "marked elevated scores on all subscales of impulsivity measured by the BIS-11" suggesting multi-component Framework B elevations (or elevations in Frameworks A, C, or

D). Further, the critical BPD-schizophrenia diagnostic confusion discussed in Chapter 2, where "many BPD behavioral phenotypes would meet criteria for schizophrenia," represents a key validation target for Framework B discrimination. The 43% BPD-schizophrenia overlap observed in this study's self-reported sample reflects this real-world diagnostic challenge, where not only impulsivity symptoms, but also psychotic features between the two disorders are *transdiagnostic*, creating profound diagnostic confusion. This multi-component elevation pattern could distinguish BPD from other disorders where impulsivity may be more circumscribed (e.g., ADHD showing primarily GNG_CE deficits) and may provide the objective behavioral differentiation needed to resolve BPD-schizophrenia diagnostic confusion where traditional symptom-based approaches fail.

Critically, as described in Chapter 2, BPD impulsivity is uniquely "active when environmental triggers and stressors are present" while ADHD deficits, for example, are not stress-dependent, supporting the need for ecological validity testing approaches. Consequently, BPD's stress-triggered impulsivity may require ecological validity testing under stress conditions (phase shift perturbations from an NDST perspective) rather than standard laboratory behavioral assessment. The reaction time optimization pattern may be particularly relevant for understanding "borderline rage" episodes—described as "hyperbolic instrumental reactive impulsive aggression" in Chapter 2—suggesting that while BPD patients have faster neural processing capabilities, these may require, for example, structured channeling through DBT mindfulness techniques rather than direct behavioral acceleration that could exacerbate impulsive outbursts. The challenge here is harnessing faster processing within appropriate regulatory frameworks rather than assuming that slowing is always optimal. The SST_OE component's role as an impulsivity-compulsivity bridge may be particularly crucial for understanding BPD's

"anger rumination" and "hypermentalization" patterns described in Chapter 2, where attention regulation failures provide the pathway through which BPD patients become trapped in ruminative cycles that escalate into impulsive acting-out behaviors.

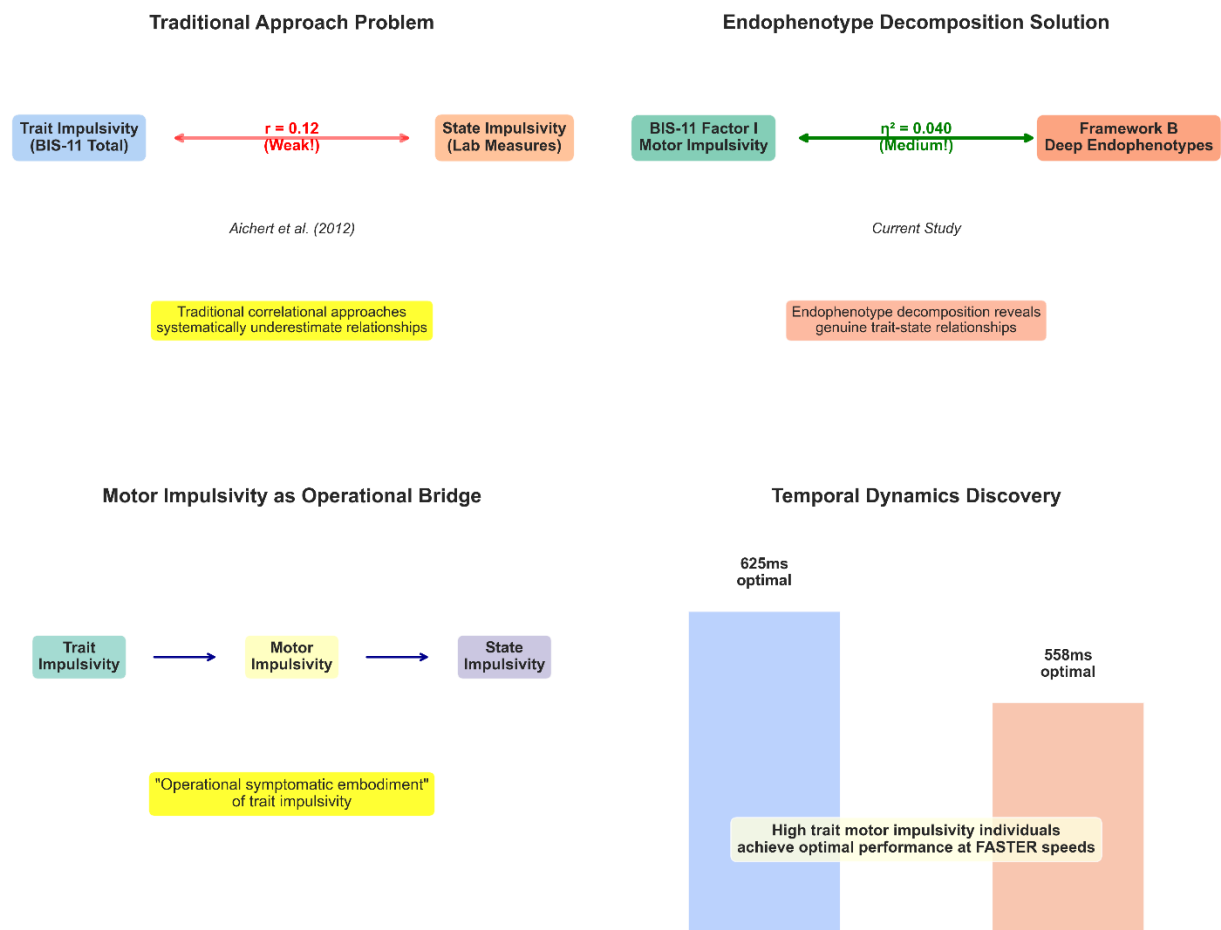
In addition, if certain subtypes (patient clusters) of BPD represent "latent schizophrenia" or fall on the "schizophrenia spectrum continuum" as suggested in Chapter 2, then Framework B patterns might reveal distinct endophenotype signatures along this developmental trajectory. Early-stage presentations of BPD might show predominantly SST_OE elevations reflecting anger rumination patterns that precede psychotic decompensation, while progressed presentations might show more pronounced NPE elevations reflecting the prefrontal cortical deterioration associated with chronic psychosis. However, the BPD-schizophrenia transition is very likely multifactorial. For example, a critical phase shift may occur when transient delusions in the form of stress-related paranoid ideation (symptom criteria 9 under diagnostic code 301.83 [F60.3] of the DSM-5-TR) become chronic and reality testing deteriorates, which may be a product of neurobiological correlates independent of those related to reaction time threshold dynamics. Nonetheless, Framework B patterns may capture the attention regulation vulnerabilities that predispose BPD to a transition to the schizophrenia behavioral phenotype, but the actual progression likely involves complex interactions between stress (perturbational) sensitivity, cognitive distortions, and neurobiological deterioration.

The multi-modal assessment approach discussed above for BPD aligns with the endophenotype hypothesis discussed in Chapter 2, where "neurobiological endophenotypes are very close to their underlying genotypes." The Framework B components may serve as intermediate phenotypes (deep endophenotypes) that bridge genetic liability (e.g., DRD4-7R variants), neural circuit dysfunction (mesocortical vs mesolimbic), and behavioral phenotype

expression. This may provide a comprehensive assessment framework that captures the full genotype→endophenotype→phenotype pathway for both impulsivity and compulsivity vulnerabilities.

Returning to impulsivity's role in BPD agnostic to delusions, the discovery of trigger sensitivity patterns, particularly relevant for understanding borderline personality disorder (BPD) presentations discussed in Chapter 2, suggests that trait motor impulsivity may determine individual sensitivity thresholds for state impulsivity activation. The framework proposed by Miskewicz et al. (2022)—that stable personality traits predict trigger perception intensity, which predicts symptom intensity—finds support in the current study's demonstration that high trait motor impulsivity individuals show characteristic state-level response patterns that differ qualitatively from low trait motor impulsivity individuals. This finding has important implications for understanding how constitutional hypersensitivity in BPD may amplify the translation from trait vulnerability to state symptom expression. With application beyond the BPD behavioral phenotype, Figure 60 shows the resolution of the trait-state discordance via the benefits of the endophenotype decomposition approach of this study to bridge these measures of motor impulsivity with the reaction time threshold discovery as a central factor.

Figure 60
Resolution of Trait-State Measurement Discordance Through Endophenotype Decomposition and Motor Impulsivity Bridge Mechanisms



Specific Treatment Implications and Recommendations for Practice. The findings of this study suggest several specific potential therapeutic modifications across behavioral phenotypes: For BPD individuals showing high Factor I trait motor impulsivity (perhaps a unique cluster or presentation of symptoms, a sub-behavioral phenotype) with optimal reaction time thresholds, DBT protocols, for example, could incorporate rapid-response skills training

rather than traditional mindfulness-based slowing techniques. For ADHD patients, high-stimulation cognitive training programs that capitalize on fast-processing strengths may prove more effective than traditional attention-focusing interventions. For ASD individuals, interventions targeting cognitive flexibility and perspective-taking may need to account for the attention regulation deficits captured by SST_OE, potentially incorporating structured transition protocols that accommodate processing differences. For schizophrenia sub-behavioral phenotypes, the severity of NPE elevations may require intensive prefrontal cortical rehabilitation approaches combined with framework-guided medication optimization. The details of these potential therapeutic modifications would need to be explored further in the field and developed via empirical testing. NPE-elevated profiles across all phenotypes suggest targeting prefrontal cortical (PFC) strengthening exercises including working memory training and cognitive flexibility protocols. Framework B profiling (and potentially other frameworks) could guide personalized intervention selection, with different treatment modules selected based on individual endophenotype patterns rather than diagnostic categories alone.

The robust discrimination achieved by Framework B components also supports the conceptualization of BRI measures as heritable endophenotypes for psychiatric illnesses as discussed in Chapter 2. The transdiagnostic nature of these effects across ADHD, ASD, schizophrenia, and BPD presentations suggests that the deep decomposed endophenotypes identified in this study represent behaviorally measurable indicators of latent neurobiological variables (features, components) as conceptualized in Chapter 2. The Framework B components serve as "directly observable endophenotypes of latent variables" in that they provide quantifiable behavioral measures of underlying cognitive control processes, supporting their

potential utility for bridging neurobiological dysfunction and behavioral phenotype expression in future multi-modal behavioral neuroscience research (Figure 61).

Figure 61
Framework B Applications Across Behavioral Phenotypes: Disorder-Specific Implications and Intervention Targets



Recommendations for Diagnostic Practice. The Framework B discrimination capabilities may have profound implications for addressing diagnostic precision challenges outlined in Chapter 2. For example, the robust differentiation between behavioral phenotypes directly addresses concerns discussed in Chapter 2 that "ADHD is potentially over diagnosed and its diagnostic criteria may indeed be too subjective" by providing objective, neurobiologically-

grounded diagnostic markers. Similarly, the consistent patterns observed across ADHD, ASD, schizophrenia, and BPD presentations provide the "finer stratification of classification" described in Chapter 2 needed to improve differential diagnosis between DSM disorders with "plural symptomatic overlap." The Framework B components (selected features) also serve as the "operational embodiments of impulsivity" described in Chapter 2 that can distinguish between disorders, particularly relevant for schizophrenia-BPD differential diagnosis where impulsivity presentations may differ qualitatively despite superficial similarities. This addresses points 14 and 15 from Chapter 2's summary applications by providing "unique diagnostic markers or endophenotypes to increase dimensionality" for improved clinical decision-making.

Behavioral Phenotype-Specific Diagnostic Applications. Framework B profiling addresses diagnostic challenges across all four behavioral phenotypes of this study while enabling crucial differential diagnosis between overlapping presentations. For ADHD, Framework B provides objective markers to address "too subjective" diagnostic criteria noted in Chapter 2, potentially distinguishing subtype-specific patterns and reducing overdiagnosis concerns while providing the "objective diagnostic criteria and finer stratification" needed for this highly prevalent but controversial diagnosis. For ASD, Framework B components may differentiate social communication deficits from repetitive behaviors, supporting dimensional rather than categorical autism conceptualizations while addressing the complexity of three-level severity classifications. For schizophrenia, Framework B may distinguish positive versus negative symptom presentations while providing objective markers during prodromal phases, potentially addressing the "most debilitating form of psychosis" (as described in Chapter 2) through earlier identification and intervention. Most critically, Framework B may resolve BPD-schizophrenia diagnostic confusion by providing objective behavioral differentiation where

traditional symptom-based approaches fail, distinguishing stress-triggered BPD reactivity from persistent schizophrenia cognitive disinhibition—a diagnostic challenge with profound treatment implications given the different therapeutic approaches required.

Framework B profiling may address the critical diagnostic challenge that "BPD patients are generally not reliable self-reporters" noted in Chapter 2. Objective behavioral endophenotype assessment could supplement traditional instruments (e.g., PAI-BOR, DIB-R) that rely on self-report accuracy. Most critically, Framework B profiling addresses the gap where traditional assessment fails to distinguish between disorders with "plural symptomatic overlap" between BPD and schizophrenia. Rather than relying on subjective symptom reporting that can be identical between these disorders, objective endophenotype assessment could provide the differential diagnostic precision that has eluded the field. The multi-component elevation pattern predicted for BPD could differentiate it from disorders showing more selective Framework B deficits - for example, distinguishing BPD's comprehensive impulsivity profile from ADHD's more circumscribed motor inhibition deficits or revealing distinct patterns that separate BPD's stress-triggered reactivity from schizophrenia's more persistent cognitive disinhibition.

The dynamic nature of trait-state relationships observed in this study reflects the NDST principle from Chapter 2 that clinical presentations emerge from "ever flowing local probability theory" where "recent prior outcomes inform future possible outcomes." The Framework B assessment approach enables clinicians to capture these dynamical phase transitions between inhibited and disinhibited states, providing the measurement foundation necessary for future NDST-informed clinical models that can predict and intervene in "temporal transitions between states" noted in Chapter 2 rather than treating static symptom profiles.

Generalizability Considerations. Several factors may limit the immediate clinical application of these findings, however. First, the substantial removal of influential cases (14.4% of the sample) through sensitivity analysis, while methodologically sound, suggests that extreme presentations may require different assessment approaches. Second, the focus on Factor I trait motor impulsivity may not capture individuals whose impulsivity primarily manifests through attentional or non-planning pathways. Third, the cross-sectional design limits causal inferences about the stability of endophenotype patterns over time. Fourth, self-reported diagnostic information requires validation through clinical assessment before applying Framework B protocols. Fifth, replication across diverse demographic populations and clinical settings will be essential before widespread implementation. Consequently, clinicians should view Framework B profiling as complementary to, rather than as a replacement for, comprehensive clinical assessment.

This framework directly enables the "fulsome endophenotype candidate gene research study" envisioned in Chapter 2's generic model, where validated behavioral deep endophenotypes serve as the foundation for integrating genetic liability, neural circuit dysfunction, and clinical behavioral phenotype expression into comprehensive assessment and treatment planning protocols. These advances directly address the "failure of reliable differential diagnosis among clinicians" noted in Chapter 1 by providing objective, deep decomposed endophenotype profiles that can distinguish between behavioral phenotypes with shared symptom presentations.

Future Research Directions. This novel theoretical framework generates testable hypotheses for future research. Studies comparing individuals with primarily impulsive disorders (ADHD, conduct disorder) versus primarily compulsive disorders (OCD, autism spectrum

repetitive behaviors) should show differential patterns of GNG versus SST performance.

Additionally, neuroimaging studies should reveal distinct neural network patterns underlying GNG (impulsivity control networks) versus SST (compulsivity control networks) performance, supporting the proposed mechanistic distinction. The empirically validated Framework B deep endophenotypes arguably provide the behavioral foundation necessary for implementing the comprehensive generic model study outlined in Chapter 2 (see next section on Recommendations for Future Research). Future research may be able to now successfully integrate genetic analysis (e.g., candidate genes and polygenic risk scores), neuroimaging (e.g., fMRI + EEG/ERP/eLORETA), and clinical assessment modalities (e.g., MMPI-II + MCMI-IV) around these empirically validated behavioral anchors, addressing the "errors and sensitivity of measurement of numerous latent variables" described in Chapter 2 that have historically limited multi-modal endophenotype research.

Resolving Literature Discordance Through Circuit-Specific Measurement

This reconceptualization directly addresses the definitional discordance noted in Chapter 2, where "some authors argued that the stop-signal task (SST) best measures prepotent response inhibition, while others argued that it was the best measure of prepotent response extinction," and where "there are still many, more recent, studies that do not make such distinctions or still confuse them." The current framework suggests that this confusion arises from attempting to force both tasks into a unitary BRI construct rather than recognizing their distinct target mechanisms. The GNG→impulsivity and SST→compulsivity mapping provides a principled resolution to this decades-long measurement debate by recognizing that both tasks measure behavioral control, but through fundamentally different neuropsychological and neurobiological (including neural network circuit system) mechanisms. This addresses the critical gap identified

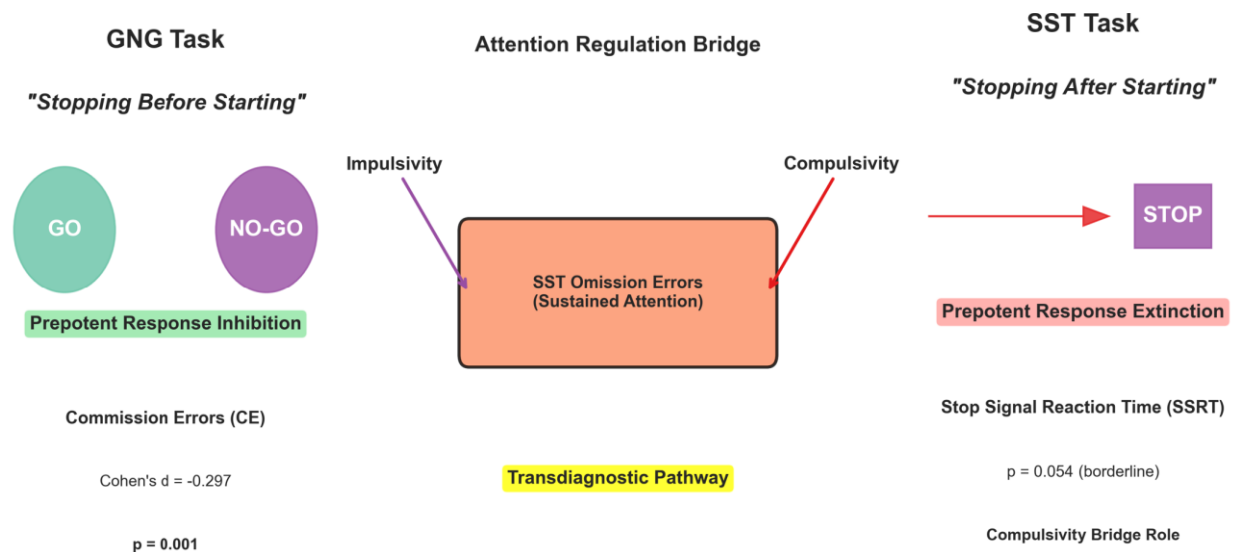
by Stahl et al. (2014) that "lack of clearly defined facets (dimensions) of impulsivity and consensus on their measurement presents a gap in the literature that urgently needs to be filled."

This resolution directly fulfills point 17 from Chapter 2's summary applications by "informing current institutional positions on impulsivity in the extant endophenotype literature." The Framework B discovery provides the "subscales that best segregate these two factors and optimize discriminant validity" that InSRI identified as a critical gap (see Chapter 2), while the GNG-impulsivity/SST-compulsivity distinction offers the "neurobiological measures that correlate with those subscales" that remained unspecified in previous frameworks. These findings also arguably directly refute the proposition from Chapter 1 that "impulsivity has been questioned as a psychological construct" due to measurement failures. The robust Framework B discrimination suggests that impulsivity remains a valid construct when appropriately decomposed and measured, addressing the fundamental challenge summarized in Chapter 1 that "both impulsivity and BRI have largely failed to meet their potential as putative endophenotypes."

This reconceptualization provides a coherent framework for understanding decades of conflicting findings while establishing clear predictions for future research validation. The theoretical reconceptualization of GNG and SST tasks provides the foundation for understanding how these behavioral measures map onto distinct neurobiological systems and pathways. Figure 62 shows this reconceptualization of the GNG models' measurement of prepotent response inhibition (action inhibition or *stopping before starting*) and the SST model's measurement of prepotent response extinction (action cancellation or *stopping after starting*) and the attention regulation bridge the two models generate between impulsivity and compuslity.

Figure 62

Theoretical Reconceptualization of Behavioral Response Inhibition Measurement Targets: GNG-Impulsivity vs. SST-Compulsivity Framework



The theoretical reconceptualization of behavioral response inhibition (BRI) measurement targets establishes the conceptual foundation for understanding how these validated deep endophenotypes map onto specific neurobiological systems and neural network pathways. Moving from the behavioral-level discoveries of this study to neurobiological validation requires examining how Framework B components correspond to established neural circuit architecture and dopaminergic pathway dysfunction patterns that underlie trait impulsivity manifestations.

Neurobiological Integration: From Dopaminergic Liability to Behavioral Expression

This study's focus on deep decomposed endophenotypes provides a mechanistic bridge between the neurobiological correlates of trait impulsivity and the behavioral manifestations of state impulsivity. The identification of NPE as a prefrontal cortical dysfunction deep endophenotype aligns with literature demonstrating that trait impulsivity involves disruptions in

mesocorticolimbic dopaminergic neural network systems. This finding is particularly significant given that motor impulsivity, as distinct from attentional or non-planning impulsivity, has been specifically linked to decreased gray matter volume in the supplementary motor area (SMA) and paracentral lobule (PCL), as discussed in Chapter 2. This study's identification of motor impulsivity-specific deep endophenotypes provides behavioral correlates for these neuroanatomically distinct motor impulsivity pathways, supporting the conceptual framework that motor impulsivity operates through unique neural circuits compared to other impulsivity facets, particularly those connecting ventral tegmental area (VTA) projections to prefrontal cortical regions (see Chapter 2). The findings from this study appear to suggest that trait-level dopaminergic dysfunction manifests as state-level prefrontal control failures when executive demands exceed individual capacity thresholds.

The robust discrimination achieved by motor impulsivity-specific deep endophenotypes across multiple behavioral phenotypes supports the unique transdiagnostic importance of motor impulsivity compared to other impulsivity types noted in Chapter 2. This specificity is exemplified, for example, by research showing that ADHD patients demonstrate marked differences in motor impulsivity, but not choice impulsivity compared to controls. This suggests that motor impulsivity may represent a particularly critical intervention target across diagnostic categories.

The transdiagnostic emergence of omission errors (OE) across GNG and SST models provides evidence for shared neurobiological vulnerabilities underlying both trait and state impulsivity across diverse behavioral phenotypes. Given the high comorbidity rates observed (e.g., 55.4% ADHD-ASD overlap, 43% BPD-schizophrenia overlap), these findings suggest that

interference control deficits may represent a common pathway through which trait impulsivity liability translates into state impulsivity manifestations across different diagnostic contexts.

However, the theoretical implications of the robust omission error (OE) effects warrant careful interpretation given the complexity of the underlying mechanisms and the study's explicit focus on the first two facets of BRI rather than the third facet (interference control). The consistent OE findings across GNG and SST models most likely represent sustained attention or vigilance deficits rather than interference control per se, indicating that attention regulation problems serve as a critical bridge mechanism between impulsivity and compulsivity vulnerabilities. This interpretation aligns with the Factor I attention and Factor II attentional impulsiveness components of the BIS-11, suggesting that sustained attention failures provide the pathway through which motor impulsivity can manifest as perseverative, compulsive-like behavioral patterns.

Rather than challenging Barkley's theoretical distinction that interference control implies cognitive rather than motor impulsivity, the OE effects support a more nuanced model where attention regulation serves as the mediating mechanism between motor and cognitive control systems. This framework suggests that while interference control (Barkley's Facet 3) remains neurobiologically distinct from prepotent response inhibition and prepotent response extinction, attention regulation deficits create vulnerability bridges that allow motor impulsivity to express through sustained attention failures, potentially explaining the transdiagnostic presentations observed across ADHD, ASD, schizophrenia, and BPD. Future research incorporating neuroimaging (e.g., fMRI) and electrophysiological measures (e.g., EEG/ERP) will be necessary to distinguish between interference control proper and attention regulation mechanisms underlying the observed deep endophenotype patterns (see next section).

The identification of distinct endophenotype patterns across Framework B components provides empirical support for the neurobiological orthogonality between BRI facets established in Chapter 2. The finding that NPE (prefrontal cortical dysfunction), GNG_CE (prepotent response inhibition), and SST_OE (attention regulation) each contribute uniquely to motor impulsivity discrimination validates the theoretical proposition that "prepotent response extinction may be neuropsychologically or symptomatically orthogonal to prepotent response inhibition." This finding also suggests that attention-related processes may operate through similarly distinct pathways.

The transdiagnostic effectiveness of Framework B components across multiple behavioral phenotypes aligns with the pleiotropy concept discussed in Chapter 2, where "a given allele confers risk to multiple phenotypes." The robust discrimination achieved across ADHD, ASD, schizophrenia, and BPD suggests that the deep decomposed endophenotypes may represent pleiotropic pathways where shared genetic vulnerabilities manifest through common cognitive control mechanisms. This "bifurcation of pleiotropic relationships by scaling down or decomposing phenotypes" (and endophenotypes) provides the pathway for "reducing or simplifying" complex genetic influences, supporting the NDST inspired proposition described in Chapter 2 that "emergent phenomena can have reductionist etiology."

The identification of distinct but interactive deep decomposed endophenotypes also aligns with NDST principles described in Chapter 2 implicit in the RDoC framework, where "a complex system comprising many elements is defined by the bidirectional interactions between and among those elements rather than by the elements themselves." The Framework B components (selected features; NPE, GNG_CE, SST_OE) may represent precisely the type of "system elements" whose interactions create the emergent properties observed in behavioral

phenotype presentations. The robust transdiagnostic effects suggest that these deep endophenotypes may exhibit the "feed-back loops between variables" and "temporal transitions between states" characteristic of complex neurobiological systems (e.g., reaction time thresholds), where "independent variables can become dependent variables and dependent variables can become independent variables" across different contexts and time scales, as noted in Chapter 2.

The mathematical implications of this variable role-switching are profound and help explain why traditional statistical approaches have failed to capture genuine trait-state relationships. When variables transition between independent and dependent roles across temporal phase states, traditional frequentist methods—which assume fixed directional relationships—become mathematically inadequate. Future NDST applications would require sophisticated mathematical frameworks including stochastic differential equation modeling to capture the random phase transitions, dynamic structural equation modeling (SEM) where the structural relationships themselves change over time, Bayesian dynamic networks to handle the shifting prior-posterior relationships, and potentially chaos theory mathematics for deterministically chaotic but apparently random transitions.

This mathematical complexity represents a computational barrier that has, as noted in Chapter 2, historically limited NDST applications in behavioral neuroscience. The Framework B deep endophenotypes may help provide the essential foundation for overcoming this barrier by offering mathematically stable, well-characterized system elements whose interactions can then be modeled using these advanced approaches. Without such precisely decomposed inputs, the mathematical complexity of modeling bidirectional variable relationships across multiple temporal scales would be computationally intractable. This underscores why the

reductionist→emergent progression outlined in Chapter 2 is not merely conceptually appealing but mathematically necessary for advancing NDST applications in computational and behavioral neuroscience. The integration of reductionist decomposition with emergent systems principles establishes both the theoretical foundation and methodological pathway for advancing computational approaches to understanding behavioral phenotypes.

Neurobiological Validation Through ERP Components. The proposed GNG-impulsivity versus SST-compulsivity distinction may generate specific predictions for N2/P3 ERP waveform component patterns discussed in Chapter 2. The N2 component (conflict monitoring/inhibition) should show differential patterns between GNG and SST contexts, with GNG-N2 reflecting rapid conflict detection characteristic of impulsivity control (stopping before you start), while SST-N2 should reflect ongoing conflict monitoring characteristic of compulsivity control (stopping after you've started). Similarly, P3 component amplitude and latency should differentiate between these mechanisms, with potential for EEG/ERP eLORETA spatiotemporal computational neuroimaging to reveal the predicted mesocortical versus mesolimbic circuit engagement patterns.

This framework addresses the gap in the literature noted in Chapter 2 that "no qEEG/ERP studies to date have examined N2/P3 amplitude or relative latencies using select outcome variables separately of each of the GNG, SST, or the WCST in groups bifurcated by trait motor impulsivity subscales of the BIS-11." The validated Framework B endophenotypes provide the precise behavioral anchors necessary for such decomposed ERP studies, potentially resolving Ford's (2014) call to "decompose the P3 to better enable its discrimination and association with candidate genes for schizophrenia," which has not been possible due to gaps in the BRI endophenotype literature.

Future neuroimaging studies utilizing eLORETA's "exact localization with zero error" capabilities arguably represent the optimal methodology for validating this theoretical framework. The millisecond temporal resolution required to distinguish *stopping before starting* versus *stopping after starting* mechanisms, combined with five-millimeter spatial precision for localizing circuit-specific activation patterns, suggests EEG/ERP with eLORETA is arguably the superior approach for differentiating impulsivity versus compulsivity control dynamics identified in this study. Moreover, the cost-effectiveness and field deployment advantages of EEG/ERP discussed in Chapter 2 would enable the large-scale well and even over-powered (such as this study was) validation studies necessary to confirm these circuit-behavior relationships across diverse populations.

Foundational Contributions to Comprehensive Multi-Modal Research. The validated deep endophenotypes identified in this study represent essential building blocks for the comprehensive multi-modal research framework outlined in Chapter 2's generic model. While this study focused on behavioral response inhibition (BRI) endophenotype decomposition due to practical constraints, the Framework B components (NPE + GNG_CE + SST_OE) provide the validated neuropsychological deep endophenotypes necessary for integration with genetic, neuroimaging, and clinical assessment modalities in future comprehensive studies.

This study exemplifies the reconciliation between reductionist and emergent approaches outlined in the Chapter 2 regarding non-linear dynamical systems theory (NDST), where "reductionism can be considered not anathema to systems thinking, but an enabler of more precise study of dynamical systems." The Framework B decomposition selected feature set arguably provides precisely the "reductionist dimensional decomposition preprocessed mathematically and empirically selected features" described in Chapter 2 as necessary for future

studies that "enable deep phenotyping and develop high-dimension neurocomputational models of impulsivity and BRI for specific behavioral phenotypes" from an emergent NDST perspective. This addresses the fundamental principle described in Chapter 2 that "neurocomputational models of complex neurobiological systems require more precise segregation and dimensionalization of system elements so as to better understand their interactions."

Resolving the Generic Model's Measurement Challenge. The generic model discussion in Chapter 2 identified a critical bottleneck: "much of the failure of RDoC endophenotype research arises from issues with the measures used (units of analysis or measure) and with identification of appropriate candidate endophenotypes." The current study directly addressed this challenge by providing empirically validated, deep decomposed endophenotypes with established discriminant validity that can serve as reliable behavioral anchors for multi-modal integration.

Addressing Literature Evolution Gaps. This study represented the next evolutionary step in the progression outlined in Chapter 2, moving beyond studies that "confound different neuropsychological measures" or "fail to make facet distinctions" to provide the dimensionalized construct measures that the literature has identified as urgently needed. The success in revealing previously masked effects (GNG_OE, SST_OE) through influence detection demonstrates how methodological precision can resolve the measurement problems that have limited endophenotype research progress.

The GNG-Impulsivity/SST-Compulsivity Framework as a Theoretical Guide. The reconceptualization of GNG and SST tasks provides the theoretical framework necessary for interpreting multi-modal findings in the generic model discussed in Chapter 2. Future studies

combining candidate genes (e.g., DRD4-7R), fMRI localization, and EEG/ERP with eLORETA, for example, can now test specific hypotheses about mesocortical circuit engagement during GNG (impulsivity control) versus mesolimbic circuit engagement during SST (compulsivity control), guided by the empirically validated behavioral endophenotypes from Framework B.

Addressing the Missing Heritability Problem Through Endophenotype

Decomposition. The validated Framework B candidate deep endophenotypes can directly address the "missing heritability problem" outlined in Chapter 2, where "the percentage of phenotypic variance that has been explained by psychiatric genetic studies is extremely low" despite high heritability estimates. This study's success in identifying robust, deep decomposed endophenotypes with established discriminant validity should help provide the precise measurement tools necessary for molecular heritability studies to detect individual gene effects that quantitative heritability studies suggest exist.

The endophenotype decomposition approach aligns with Chapter 2's proposition that "as one continues to decompose an endophenotype, one arguably should get closer to monogenic Mendelian etiology," since Framework B components may each "implicate fewer susceptibility genes or risk alleles than the behavioral phenotype." This decomposition strategy addresses points 2, 4, 5, and 7 from Chapter 2's gap analysis discussed in that chapter's summary by providing the measurement precision necessary for "identifying individual risk alleles that have relatively large effect" and "resurrecting the candidate gene literature" (and RDoC's first unit of measure, genes) through improved endophenotype-genotype coupling.

Enabling Neurocomputational Digital Twin Development. The validated deep endophenotypes and theoretical framework established in this study provide essential foundation components for developing AI-enabled neurocomputational models outlined in Chapter 2. The

Framework B selected feature set (NPE + GNG_CE + SST_OE) offers precisely the type of dimensionalized construct measures identified in Chapter 2 as necessary for reliable machine learning (ML) applications, while the GNG-impulsivity/SST-compulsivity distinction provides the theoretical structure needed for interpretable (explainable) AI (XAI) models in clinical contexts (see final section of this Chapter).

This advancement directly addresses the fundamental principle from Chapter 2 that "better inputs result in better outputs" in neurocomputational models. The validated endophenotypes provide the "reductionist dimensionally decomposed empirically and mathematically selected features" identified as necessary for "high-dimension neurocomputational models of impulsivity and BRI." The Framework B components represent precisely the type of "more precise segregation and dimensionalization" required for understanding complex neurobiological system interactions, addressing the gap noted in Chapter 2 where "neurocomputational models of complex neurobiological systems require more precise segregation and dimensionalization of system elements so as to better understand their interactions."

As noted in Chapter 2, "discriminated inputs should lead to discriminated outputs" in neurocomputational models, and the current study's success in identifying robust, influence-resistant deep endophenotypes addresses the data quality requirements for digital twin development of behavioral phenotypes. The validated deep endophenotypes provide the "higher quality and better discriminated input variables" necessary for reliable neurocomputational modeling of transdiagnostic psychological constructs as well as behavioral phenotypes. These deep decomposed endophenotypes also enable the development of "computational assays that can be mapped onto neuropsychological and neurobiological data obtained from clinical and

neurotypical populations“ for differential diagnosis, directly addressing points 19, 20, and 21 from Chapter 2's summary applications.

The successful reconciliation of reductionist endophenotype decomposition with the emergent NDST perspective outlined in Chapter 2 also provides the methodological foundation for sophisticated digital twin development. By demonstrating that “emergent phenomena can have reductionist etiology,” this study enables neurocomputational models that can capture both the detailed component-level mechanisms (Framework B deep endophenotypes) and the complex system-level dynamics (behavioral phenotype expressions) necessary for clinically relevant digital twins. Specific applications and detailed recommendations for implementing these digital twin approaches are discussed in the Recommendations for Future Research section later in this Chapter 5.

The transition from this study's reductionist endophenotype decomposition to future NDST-informed digital twin development represents the natural progression outlined in Chapter 2, moving from “elemental studies“ to “emergent complex neurobiological systems studies.” The validated Framework B components provide the precisely dimensionalized system elements necessary for NDST models that focus on “bidirectional interactions between and among those elements rather than by the elements themselves.” This enables digital twins that capture the “emergent properties that cannot be quantified via an elemental summation” but emerge from the complex interactions between decomposed endophenotypes across temporal and contextual dimensions. The neurobiological validation of decomposed endophenotypes establishes the foundation for translating these research findings into practical clinical assessment and intervention approaches.

Clinical Implications: Integrating Trait Assessment with State Measurement

These findings have substantial implications for resolving the clinical assessment dilemma created by weak trait-state correlations discussed in Chapter 2. Rather than viewing self-report and laboratory behavioral measures as assessing fundamentally different constructs, as the literature suggests, this study's results support integrated assessment protocols that combine trait-level screening (e.g., BIS-11 Factor I trait motor impulsivity) with state-level deep endophenotype profiling (e.g., Framework B components). This approach provides both the temporal stability needed for clinical characterization and the dynamic sensitivity required for intervention targeting.

The discovery of trigger sensitivity patterns, particularly relevant for understanding borderline personality disorder (BPD) presentations, suggests that trait motor impulsivity may determine individual sensitivity thresholds for state impulsivity activation. The framework proposed by Miskewicz et al. (2022)—that stable personality traits predict trigger perception intensity, which predicts symptom intensity—finds support in the current study's demonstration that high trait motor impulsivity individuals show characteristic state-level response patterns that differ qualitatively from low trait motor impulsivity individuals. This finding has important implications for understanding how constitutional hypersensitivity in BPD, for example, may amplify the translation from trait vulnerability to state symptom expression.

Methodological Innovation: A Template for Future Trait-State Integration Studies

The methodological innovations employed in this study—extreme groups design, Cook's distance leverage-residual (influence) sensitivity analysis, and cross-model convergent analysis—provide a template for future research aimed at resolving trait-state measurement discordance across the matrix of RDoC cognitive control and sensory motor systems domains

and neural circuit, behavioral, self-report, and paradigm units of analysis. The success of these approaches in revealing previously masked effects (GNG_OE, SST_OE) suggests that methodological rigor, rather than construct revision, may be the key to understanding trait-state relationships. Future studies investigating the temporal dynamics between stable personality traits and dynamic behavioral responses would benefit from adopting similar decomposition and sensitivity analysis approaches to maximize detection of genuine but potentially subtle trait-state correspondences.

The success of the endophenotype decomposition approach also validates the International Society for Research on Impulsivity (InSRI) framework discussed in Chapter 2, which identified prepotent response inhibition (measured by the GNG task) and prepotent response extinction (measured by the SST) as neurobiologically and conceptually distinct subtypes of motor impulsivity (but see impulsivity-compulsivity bridge discussion above). However, this study advances beyond the InSRI recommendations by identifying specific self-report and laboratory behavioral instrument subscales and endophenotypes (Framework B) that optimize discriminant validity—addressing the gap noted in Chapter 2 that InSRI had not identified which subscales best segregate these factors.

This finding also supports the BIS/BAS theoretical framework outlined in Chapter 2, where “an overactive behavioral activation system or an underactive behavioral inhibition system associates with impulsivity.” This study's demonstration that trait motor impulsivity translates into specific state-level behavioral patterns arguably provides empirical evidence described in Chapter 2 for how “lack of behavioral response inhibition (disinhibition) or a deficit in the behavioral inhibition system (BIS) can enable or increase impulsivity via the behavioral activation system (BAS).”

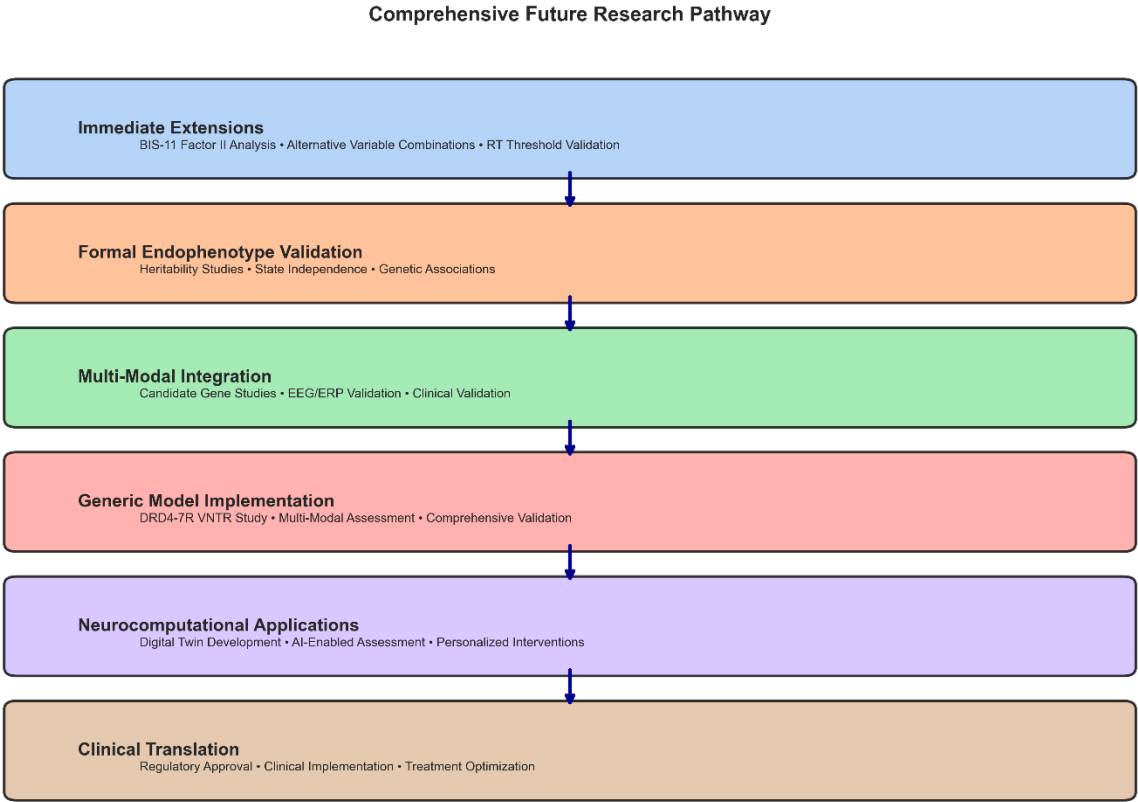
The methodological progression from traditional correlational approaches to extreme groups analysis with endophenotype decomposition also reflects the evolution toward systems thinking outlined in Chapter 2. While this study employed reductionist analytical methods, the resulting validated deep decomposed endophenotypes help provide the precise system components necessary for future NDST applications in behavioral neuroscience. This exemplifies how "reductionism enables more precise study of dynamical systems" by providing the well-characterized elements whose interactions can then be studied using emergent systems approaches.

Recommendations for Future Research

The empirically validated Framework B deep decomposed endophenotypes (NPE + GNG_CE + SST_OE) and theoretical advances established in this study should provide a robust foundation for an extensive research program spanning empirical validation, multi-modal integration, and advanced neurocomputational applications (e.g., XAI digital twins). The successful demonstration that endophenotype decomposition can help resolve trait-state measurement discordance while revealing genuine behavioral control mechanisms creates opportunities for transformative advances across behavioral neuroscience, psychiatric genetics, and computational psychiatry. The following recommendations progress systematically from immediate empirical extensions through complex multi-modal studies mirroring that progression in the literature review covered by Chapter 2, culminating in advanced neurocomputational AI applications that leverage these validated deep endophenotypes for next-generation research, diagnostic, and clinical tools (Figure 63).

Figure 63

Comprehensive Future Research Program: From Immediate Extensions to Clinical Translation and Neurocomputational Applications



While Framework B emerged as the optimal combination in the current study, the statistical significance of alternative frameworks (A, C, and D) indicates they capture meaningful variance in motor impulsivity discrimination. Rather than limiting future research to Framework B alone, comprehensive validation requires systematic comparison across all four frameworks to establish their relative advantages for specific populations, behavioral phenotypes, clinical contexts, and neurocomputational models. This multi-framework approach strengthens the overall contribution of this study by demonstrating that the study identified not just one optimal

solution, but a systematic methodology for endophenotype optimization and deep endophenotype discovery that can be adapted across diverse research and clinical applications.

Immediate Empirical Extensions

The most immediate research priorities involve leveraging the existing robust dataset and methodological innovations to expand understanding of impulsivity dimensionality and endophenotype optimization. These extensions require minimal additional resources while providing critical validation of the decomposition approach across different impulsivity facets and variable (feature) combinations.

Expanding BIS-11 Factor Analysis. The current study's focus on BIS-11 Factor I trait motor impulsivity, while theoretically grounded and empirically successful, represents only one dimension of the multifaceted impulsivity construct. Future research should extend these analyses to Factor II motor impulsiveness and BIS-11 total scores using the existing robust overpowered dataset. As the data necessary for these analyses has been collected, direct comparison of endophenotype discrimination across different impulsivity dimensions is relatively facile. These analyses would test whether the attention-motor combination in Factor II shows different Framework B patterns compared to pure Factor I trait motor impulsivity, potentially revealing how attentional components modify behavioral control mechanisms (see previous discussion in the Implications section). Additionally, statistical analysis BIS-11 total scores could determine whether composite impulsivity measures obscure or enhance endophenotype relationships, providing critical insights into the measurement precision versus comprehensiveness (and dimensional reduction) trade-off in endophenotype research.

Alternative Variable Combinations. While the current study selected nine variables based on extensive literature review suggesting optimal differentiation with trait motor

impulsivity, systematic exploration of alternative variable combinations could reveal additional robust endophenotypes. Future studies can examine, for example, WCST perseverative errors (PE) versus non-perseverative errors (NPE) to determine whether different error types provide differential discrimination. The WCST learning-to-learn variable also warrants particular investigation as it may capture adaptive flexibility mechanisms distinct from the executive dysfunction reflected in NPE.

Alternative GNG and SST variable combinations (e.g., reaction time variability, post-error slowing) could identify additional state impulsivity markers. With respect to the SST, a variable reflecting the impact of participant frustration (e.g., impatient impulsiveness) with the regression towards the mean feature that forces a 50% success rate, could be developed to quantify the impact on the instrument's validity, particularly to tease out any potential discordance effects between neurotypical (low impulsivity or low compulsivity) controls and treatment groups with high impulsivity and/or high compulsivity. Further, Cross-Model variable combinations not tested in Framework B (e.g., NPE + SSRT + GNG reaction time) might reveal novel deep endophenotype patterns with different theoretical implications.

Reaction Time Threshold Validation Studies. The discovery of differential speed-accuracy optimization patterns via a reaction time threshold (558ms vs 625ms) represents one of this study's most clinically significant findings, challenging conventional *slow down* intervention approaches. Priority validation studies should replicate these reaction time threshold effects across independent samples and diverse laboratory behavioral paradigms. Neurophysiological validation studies should examine the relationship between individual N2 ERP component timing (200-270ms) and reaction time threshold optimization patterns (558ms vs 625ms) to test the proposed sequential processing model directly. Combined EEG/ERP and behavioral

assessment protocols could establish whether N2 latency variations predict individual reaction time threshold profiles, providing mechanistic validation for the neural efficiency hypothesis underlying differential speed-accuracy optimization. These multimodal studies would strengthen the neurobiological foundation for reaction time threshold profiling by demonstrating direct correspondence between established neurophysiological endophenotypes and novel behavioral optimization markers.

Cross-task validation studies should examine whether the 558ms optimization pattern emerges consistently across different inhibitory control measures beyond the GNG task, including Stroop, flanker, and Simon tasks. Population validation studies should test whether the reaction time threshold difference generalizes across age groups, given that this study's sample was limited to ages 18-40 and prefrontal cortical development continues into the mid-twenties. Clinical validation studies should examine whether individuals with confirmed high trait motor impulsivity diagnoses show consistent 558ms optimization patterns, while intervention studies should test whether treatments designed to work with (rather than against) faster processing optimization improve outcomes compared to traditional approaches. These validation studies would establish reaction time threshold profiling as a reliable clinical tool for personalizing intervention strategies across behavioral phenotypes.

Mixed Phenotype Validation Studies. The discovery of choice impulsivity presentations within low motor impulsivity groups requires systematic validation through studies that simultaneously assess multiple impulsivity dimensions using both self-report and behavioral measures, potentially revealing additional phenotypic subtypes that inform personalized intervention approaches across behavioral phenotypes.

Formal Endophenotype Validation Studies. While this study has identified robust candidate deep decomposed endophenotypes through Framework B components, formal classification as endophenotypes requires systematic validation against established criteria outlined in Chapter 2. The current findings demonstrate reliable behavioral discrimination and theoretical coherence, but the aspirational goal of establishing these measures as true endophenotypes necessitates comprehensive validation studies addressing the multiple criteria proposed by Gottesman and Gould (2003), Cannon and Keller (2006), and Jablensky's (2009) integrated framework.

Heritability and Family Studies. Priority validation studies should establish the heritability of Framework B components, with secondary analyses examining Frameworks A, C, and D to determine whether different endophenotype combinations show varying heritability patterns or population-specific advantages through twin, adoption, or family-based designs. As outlined in Chapter 2, endophenotypes must demonstrate co-segregation within families and higher prevalence in unaffected relatives of probands compared to the general population. Family studies examining NPE, GNG_CE, and SST_OE performance across parents, siblings, and offspring of individuals with high trait motor impulsivity would test whether these measures meet Gottesman and Gould's criteria for familial transmission. Twin studies could establish quantitative heritability estimates while determining whether Framework B components show the "modest to large effect sizes" and "normally distributed traits in the population" specified in Jablensky's comprehensive criteria.

State Independence Validation. Critical to endophenotype classification is demonstrating state independence—that Framework B components remain stable across clinical states and detectable prior to symptom onset. Longitudinal studies tracking these measures across remission

and exacerbation periods in individuals with ADHD, ASD, schizophrenia, and BPD would establish whether they represent stable traits rather than state-dependent markers. Prodromal studies examining Framework B patterns in at-risk individuals before symptom emergence would test whether these measures serve as the "early predictors or primordial diagnostic markers" fundamental to the endophenotype concept discussed in Chapter 2.

Mediational Versus Liability-Index Model Testing. Future research must determine whether Framework B components operate through mediational or liability-index models described in Chapter 2. Mediational model testing would require demonstrating that interventions targeting NPE, GNG_CE, or SST_OE directly modify downstream behavioral phenotypes. Liability-index model validation would establish that genetic variants independently influence both Framework B components and behavioral phenotypes through pleiotropic pathways. Statistical genetics approaches including path analysis and structural equation modeling (SEM) could distinguish between these models, with implications for whether Framework B components qualify as intermediate phenotypes (mediational) or risk indicators (liability-index) under Chapter 2's theoretical framework.

Genetic Association Validation. Establishing Framework B components (features) as true endophenotypes rather than biomarkers requires demonstrating their genetic etiology as emphasized in Chapter 2. Candidate gene studies examining associations between Framework B performance and established polymorphisms (e.g., DRD4-7R, COMT Val158Met) would provide initial validation, while polygenic risk score (PRS) analyses could test whether these measures demonstrate stronger genetic associations than composite behavioral phenotypes. The prediction from Chapter 2's decomposition theory is that deep endophenotypes should demonstrate "larger genotype association effect sizes than behavioral phenotypes" and

potentially approach the monogenic decomposition that represents the ultimate goal of endophenotype research.

Successful validation of Framework B components (features) as formal deep endophenotypes would transform them from promising behavioral markers into validated intermediate phenotypes meeting the rigorous criteria established in the psychiatric genetics literature. This validation is prerequisite to the sophisticated multi-modal studies outlined below, as true endophenotype status provides the theoretical foundation necessary for candidate gene resurrection, neuroimaging validation, and neurocomputational digital twin development discussed in subsequent sections.

Behavioral Phenotype Group Analyses. The current study's robust dataset includes substantial self-reported representation across the four key behavioral phenotypes (ADHD ~20%, ASD ~12%, schizophrenia ~4%, BPD ~10%) that is the focus of this study, as well as an additional 32 Axis I and Axis II behavioral phenotypes that also implicate impulsivity. This enables immediate between-groups comparative analyses using Framework B's deep decomposed endophenotypes as dependent variables. Future analyses could examine whether Framework B profiles (or other Framework profiles from Chapter 4) differentiate behavioral phenotype groups beyond the trait motor impulsivity effects demonstrated in this study. These analyses would test group-specific endophenotype patterns (e.g., whether ADHD groups show predominantly GNG_CE deficits while ASD groups show SST_OE patterns) and validate the transdiagnostic versus DSM disorder-specific nature of attention regulation bridges proposed in the theoretical framework. These behavioral phenotype differentiation studies could also inform additional multimodal feature selection and engineering for neurocomputational AI digital twin development.

ADHD-Specific Phenotype Analyses. Given ADHD's status as the *poster child of impulsivity*, specific analyses should examine whether the three ADHD subtypes show distinct framework patterns: predominantly inattentive type potentially favoring attention-focused frameworks (A, C, or D), hyperactive-impulsive type showing optimal Framework B discrimination, and combined type requiring multi-framework approaches. The high prevalence of ADHD in this sample (21%) provides adequate power for subtype-specific analyses that could inform the diagnostic precision challenges noted in Chapter 2.

ASD-Specific Compulsivity Bridge Analyses. ASD's unique position bridging impulsivity and compulsivity through "restricted, repetitive patterns of behavior" makes it critical for validating the SST as an impulsivity-compulsivity bridge. Analyses should examine whether ASD severity levels (1-3) discussed in Chapter 2 show systematic Framework patterns, with particular attention to SST_OE as a marker of the attention regulation failures underlying both social communication deficits and repetitive behaviors.

Schizophrenia-Specific Severity Analyses. Given schizophrenia's severity ("BRI deficits as bad or worse as impulse control disorders" as noted in Chapter 2), analyses should test whether Framework B shows ceiling effects requiring alternative frameworks. Symptom cluster analyses (positive vs. negative symptoms using PANSS factors) could determine whether different frameworks associate with different symptom presentations, supporting the diagnostic flexibility observed in schizophrenia presentations.

BPD-Specific Spectrum Analyses. BPD's complex presentation with "elevated scores on all subscales of impulsivity" (as described in Chapter 2) and potential spectrum relationship with schizophrenia requires specialized analyses the data of this study and future research examining

whether BPD subtypes (internalizing vs. externalizing, ego-syntonic vs. ego-dystonic) show distinct Framework patterns that might predict spectrum progression risk.

Limitations of Self-Report Diagnosis. It is important to note that critical limitations of self-reported diagnostic classification must be acknowledged in interpreting these analyses. The behavioral phenotype groupings from this study reflect participant self-identification as being clinically diagnosed rather than direct clinical diagnosis, potentially introducing classification errors that could attenuate or distort true group differences. Framework B patterns observed in self-reported groups would require validation through follow-up studies using clinically diagnosed patient groups or participants assessed with instruments explicitly designed and validated for DSM disorder diagnosis (e.g., SCID-5, MINI, disorder-specific rating scales) to confirm, ratify, or revise any self-reported clinical diagnosis. Consequently, these immediate analyses using the data set from this study should be viewed as preliminary hypothesis-generating studies that identify promising patterns requiring subsequent clinical validation. Successful replication in clinically diagnosed samples would establish Framework B profiling as a valid transdiagnostic assessment tool, while divergent patterns might reveal important differences between self-perceived (with impure reporting of clinical diagnosis) and directly clinically diagnosed presentations that inform our understanding of disorder phenomenology and endophenotype expression.

Demographically Classified Study Group Analysis. Similarly, the existing dataset also enables demographic stratification analyses across gender, race, and ethnicity groupings to examine whether Framework B (and perhaps other frameworks) discrimination patterns generalize across diverse populations. These demographic analyses are particularly important given the documented phylogenetic variation in DRD4-7R VNTR polymorphism prevalence

across populations. The DRD4-7R allele shows marked population differences across ethnic and geographic groups, with this phylogenetic distribution pattern hypothesized to relate to historical migration patterns and environmental adaptation pressures resulting in evolutionary survival focused risk seeking behavioral adaptations. Such genetic architecture differences across populations suggest that Framework B deep decomposed endophenotype patterns may show population-specific variations that reflect underlying neurobiological diversity. These analyses could reveal cultural or biological moderators of endophenotype expression while testing the universality of the impulsivity-compulsivity bridge mechanisms across genetically diverse populations. Unequal group sizes necessitate appropriate statistical approaches (e.g., bootstrapping, weighted analyses) but provide sufficient power for meaningful effect detection given the robust original sample size.

Multi-Modal Integration Studies: Implementing the Generic Model

Building on the empirical foundation established through immediate extensions, the next phase involves integrating Framework B deep decomposed endophenotypes (features) with genetic, neuroimaging, diagnostic, and clinical assessment modalities. These multi-modal studies represent the critical bridge between behavioral endophenotype identification and comprehensive neurobiological validation, moving toward the full generic model outlined in Chapter 2.

Candidate Gene Integration. The validated Framework B deep decomposed endophenotypes may provide the behavioral anchors necessary for resurrecting candidate gene research and potentially reviving the RDoC's currently frozen *genes* unit of measure. Future studies can examine dopaminergic system polymorphisms (e.g., DRD2, DRD4-7R, DRD5, DAT1) and catecholaminergic pathway variants (e.g., MAOA, COMT Val158Met) in relation to Framework B deep endophenotype performance. Comparative analyses across all four

frameworks identified in Chapter 4 would determine whether specific genetic variants show differential associations with alternative endophenotype combinations, potentially revealing genotype-specific optimal frameworks for different populations. The DRD4-7R polymorphism discussed in detail in Chapter 2 deserves particular attention given its established associations with ADHD and impulsivity, while COMT Val158Met variants may show differential associations with NPE (prefrontal cortical dysfunction) versus GNG_CE (motor inhibition) components. Polygenic risk scores (PRS) discussed in Chapter 2 for ADHD, ASD, schizophrenia, and BPD can be correlated with Framework B profiles to test whether deep decomposed endophenotypes capture genetic liability more precisely than composite measures.

Neuroimaging Validation Studies. The theoretical predictions generated by this study's GNG-impulsivity/SST-compulsivity framework require direct neurobiological validation through simultaneous EEG/ERP and laboratory behavioral assessment. High-priority studies should employ eLORETA spatiotemporal computational neuroimaging analysis to test whether GNG commission errors (CE) engage mesocortical dopaminergic pathways (VTA→PFC) optimized for rapid decision-making, while SST omission errors (OE) engage attention regulation networks with differential temporal dynamics. N2/P3 component and waveform analysis could examine whether GNG-N2 reflects rapid conflict detection ("stopping before starting") versus SST-N2 reflecting sustained conflict monitoring ("stopping after starting"). Complementary fMRI studies could provide spatial validation of predicted mesocortical versus mesolimbic circuit engagement patterns, though, as discussed in Chapter 2, the superior temporal resolution of EEG/ERP makes it the optimal methodology for distinguishing the millisecond-level dynamics hypothesized in this study.

Behavioral Phenotype-Specific Neuroimaging Priorities. Different behavioral phenotypes may require targeted neuroimaging approaches: ADHD studies should focus on frontoparietal and frontostriatal circuit engagement during Framework B tasks, ASD studies should examine ACC-mPFC and insula dysfunction patterns, schizophrenia studies should test dopamine hypothesis predictions across positive/negative symptom clusters, and BPD studies should investigate stress-triggered circuit activation patterns under ecological validity conditions.

Clinical Validation and Diagnostic Studies. Translating Framework B deep decomposed endophenotypes (features) into clinically useful tools requires systematic validation against established diagnostic instruments and longitudinal stability assessment. These studies will determine whether deep decomposed endophenotypes can enhance differential diagnosis precision and provide reliable trait markers across developmental periods.

Robust Diagnostic Validation. The Framework B components (features) require validation against gold-standard clinical assessment instruments to establish their utility for differential diagnosis. Priority studies should correlate Framework B profiles with MMPI-2-RF clinical scales, for example, to determine whether endophenotype patterns predict specific psychopathology dimensions. The Millon Clinical Multiaxial Inventory-IV (MCMI-IV) associations would test whether Framework B components (features) differentiate personality disorder presentations, particularly relevant for the SST-compulsivity bridge mechanism proposed for understanding repetitive behaviors in autism (ASD) and obsessive-compulsive (OCD) presentations. Structured clinical interviews (e.g., SCID-5, MINI) should validate self-reported diagnostic classifications used in the current study, with particular attention to diagnostic boundary cases where Framework B profiling might provide objective criteria for differential diagnosis.

ADHD-Specific Diagnostic Validation. Framework B validation in ADHD samples should address the "too subjective" diagnostic criteria noted in Chapter 2 by correlating endophenotype patterns with objective measures of attention (CPT-3, TOVA) and hyperactivity/impulsivity (Achenbach scales, Conners' Rating Scales). Subtype-specific validation should test whether Framework patterns can distinguish predominantly inattentive, hyperactive-impulsive, and combined presentations more reliably than current subjective criteria. Comorbidity studies should examine whether Framework B can differentiate ADHD from the high-comorbidity disorders (ODD, anxiety, depression) noted in Chapter 2.

ASD-Specific Diagnostic Validation. ASD validation studies should correlate Framework B patterns with gold-standard diagnostic instruments (ADOS-2, ADI-R) while examining whether endophenotype profiles can differentiate the three severity levels and distinguish social communication deficits from repetitive behaviors. Given ASD's high comorbidity with ADHD (37-85%), particular attention should focus on whether Framework patterns can achieve differential diagnosis between these overlapping presentations.

Schizophrenia-Specific Diagnostic Validation. Schizophrenia validation requires correlation with PANSS factors and assessment of whether Framework B patterns can distinguish positive versus negative symptom presentations. Prodromal studies using instruments like SIPS (Structured Interview for Prodromal Syndromes) should test whether Framework patterns can predict conversion risk and provide early intervention targets.

BPD-Specific and BPD-Schizophrenia Differential Validation Studies. The most critical validation priority is establishing Framework B's capacity to differentiate BPD from schizophrenia—addressing the diagnostic confusion discussed in Chapter 2 where "many BPD behavioral phenotypes would meet criteria for schizophrenia." Priority validation studies should

examine Framework B performance in clinically diagnosed BPD samples using stress-induction paradigms to test the stress-sensitivity that distinguishes BPD impulsivity from other DSM disorders. Head-to-head comparison studies using clinically diagnosed BPD versus schizophrenia samples must test whether Framework B (or Frameworks A, C, or D) patterns can achieve the differential diagnostic precision that symptom-based approaches cannot.

Framework B (or Framework A, C, D) profiles should be correlated with BPD-specific instruments discussed in Chapter 2 including the Personality Assessment Inventory-Borderline Features Scale (PAI-BOR), Diagnostic Interview for Borderlines-Revised (DIB-R), State-Trait Anger Expression Inventory-2 (STAXI-2), Pathological Narcissism Inventory (PNI), and Psychopathic Personality Inventory-Revised (PPI-R) to validate endophenotype patterns against established BPD measures. Studies should examine whether Framework B (or other Framework) components show differential associations with BPD's three symptom domains (cognitive distortions [thinking], emotional dysregulation [feeling], impulsive behavior [acting]) and whether stress-induction protocols reveal different Framework B (or other Framework) response patterns: BPD showing stress-triggered elevation patterns versus schizophrenia showing more stable, baseline elevations.

Spectrum validation studies should test whether Framework B (or other Frameworks from Chapter 4) deep endophenotypes map onto the proposed "schizophrenia spectrum continuum" with BPD as "latent schizophrenia" as discussed in Chapter 2. Longitudinal studies tracking individuals from BPD diagnosis through potential progression to schizotypal or psychotic presentations could establish whether Framework B (or other Framework) patterns predict trajectory risk and identify the critical transition points along the spectrum.

Longitudinal Stability and Developmental Studies

The endophenotype concept requires demonstration of temporal stability across developmental periods and clinical states. Longitudinal studies tracking Framework B components across months to years would establish their reliability as trait markers versus state-dependent fluctuations. Developmental studies examining Framework B patterns across childhood, adolescence, and adulthood could test whether these endophenotypes serve as the "early predictors or primordial diagnostic markers" outlined in Chapter 2's endophenotype framework. Further, family studies examining Framework B heritability patterns could provide critical validation of their genetic foundations and potential utility for identifying at-risk individuals before symptom emergence.

Comparative Framework Validation Studies

While Framework B demonstrated optimal performance in the current study, the statistical significance of Frameworks A, C, and D suggests that they may provide superior discrimination for specific clinical contexts or populations. For this reason they are often parenthetically suggested in the above recommendations. Systematic comparison studies should examine framework performance across different behavioral phenotypes to determine whether ADHD presentations show optimal discrimination with Framework B, while ASD or schizophrenia might benefit from alternative combinations. Clinical validation studies could test framework-specific hypotheses: for example, whether Framework A (NPE + GNG_CE + SSRT) provides superior discrimination for primarily motor-impulsive presentations, while Framework C might excel for attention-dysregulated profiles. These comparative studies would establish clinical decision rules for selecting optimal frameworks based on presenting symptoms, demographic characteristics, or suspected underlying mechanisms. Rather than weakening the

Framework B discovery, comparative validation would establish the current study's contribution as identifying not just one optimal combination, but a systematic approach to deep endophenotype selection that can be tailored to specific clinical and research contexts.

Behavioral Phenotype Stratification Studies

The high self-reported comorbidity rates and RDoC validating transdiagnostic effects observed in this study suggest that Framework B's deep decomposed endophenotypes may reveal behaviorally coherent subgroups (clusters) that transcend traditional diagnostic boundaries. These stratification studies will test the RDoC premise that dimensionally-defined endophenotypes provide more valid intervention targets than categorical diagnostic approaches.

Within-Diagnosis Endophenotype Profiling. The current study's high comorbidity rates (55.4% ADHD-ASD overlap, 43% BPD-schizophrenia overlap) suggest that traditional diagnostic categories may obscure meaningful endophenotype subgroups, which is consistent with the RDoC framework rationale. Future research could examine within-diagnosis Framework B variability to identify behaviorally coherent subgroups that may represent distinct etiological pathways. This is somewhat prophetic for application of machine learning classifiers and clustering approaches that deploy the benefits of robust pattern recognition found in sophisticated AI methods (see section on neurocomputational applications below).

ADHD Subtype Stratification. ADHD samples stratified by Framework B profiles might reveal predominantly motor-impulsive versus attention-dysregulated subtypes requiring different intervention approaches. Given ADHD's three recognized subtypes, future research should test whether Framework patterns provide finer discrimination than current DSM categories, potentially identifying subgroups that predict treatment response to stimulant versus non-stimulant medications or behavioral versus cognitive interventions.

ASD Severity and Presentation Stratification. Autism spectrum disorder (ASD) analyses could test whether Framework B patterns differentiate individuals with primarily repetitive behaviors versus social communication deficits, supporting dimensional rather than categorical ASD conceptualizations. The three severity levels may show systematic Framework patterns that could inform individualized intervention approaches, while high-functioning ASD individuals (primarily Aspergers type) may show distinct profiles from those with intellectual disability.

Schizophrenia Symptom Cluster Stratification. Schizophrenia's symptom heterogeneity suggests that Framework patterns may differentiate positive symptom-predominant versus negative symptom-predominant presentations, early-onset versus late-onset cases, or treatment-responsive versus treatment-resistant subtypes. The PANSS five-factor model (positive, negative, disorganized, excited, depressed) could guide stratification analyses to determine whether Framework patterns map onto these established symptom dimensions.

BPD Complexity Stratification. BPD's heterogeneity requires specialized stratification examining internalizing versus externalizing subtypes, ego-syntonic versus ego-dystonic presentations, and comorbidity patterns with other Cluster B disorders. Studies should examine whether different BPD subtypes show distinct Framework B patterns: for example, whether externalizing BPD shows predominantly GNG_CE elevations while internalizing BPD shows SST_OE prominence. Analyses of BPD comorbid with malignant narcissism (BPD+NPD+ASPD), including the dark triad subtype, could test whether these extreme presentations show Framework B patterns that approach ceiling effects across all components, potentially requiring alternative assessment approaches.

Transdiagnostic Endophenotype Clusters. Data-driven clustering research and related analysis using Framework B components across diagnostic categories could identify naturally

occurring endophenotype profiles that transcend traditional diagnostic boundaries. Machine learning approaches (k-means clustering, latent profile analysis) applied to Framework B × behavioral phenotype matrices might reveal biologically coherent subgroups (computational phenotypes) that better predict treatment response than diagnostic labels alone. These analyses would test the RDoC premise described in Chapter 2 that dimensionally-defined endophenotypes provide more valid targets for intervention than symptom-based diagnostic categories. Machine learning approaches applied to all four framework combinations might reveal that different frameworks capture distinct transdiagnostic clusters, with some individuals showing optimal discrimination through Framework B while others require alternative combinations.

Spectrum and Comorbidity Mapping Studies. The finding that psychotic features are *transdiagnostic* between BPD and schizophrenia requires specialized Framework B validation to determine whether endophenotype patterns can distinguish what symptom-based approaches cannot. Studies should examine whether Framework B discrimination persists even during active psychotic episodes when symptom overlap is maximal. Spectrum mapping studies should test the hypothesis that Framework B components show systematic changes along the proposed BPD→schizotypal→schizophreniform→schizophrenia continuum. Machine learning classification of BPD subtypes and spectrum positions based on Framework B profiles could inform whether dimensional endophenotype approaches can capture complex BPD taxonomy and spectrum relationships more effectively than traditional categorical methods. Similarly, the high ADHD-ASD comorbidity (37-85%) warrants studies examining whether Framework patterns can distinguish *pure* ADHD from *pure* ASD versus truly comorbid presentations, potentially resolving diagnostic confusion in this high-overlap population.

Methodological Advancement Studies

The methodological innovations employed in this study—particularly Cook's distance leverage-residual (influence) sensitivity analysis and extreme groups design—require systematic validation across diverse research contexts to establish their broader utility in behavioral neuroscience. These studies will determine whether the analytical approaches that revealed Framework B effects can enhance detection of genuine relationships in other cognitive domains.

Cook's Distance Sensitivity Analysis Validation. The substantial impact of influence sensitivity analysis in revealing previously masked effects requires systematic validation across diverse behavioral neuroscience contexts. Future studies could apply Cook's distance leverage-residual (influence) analysis to existing datasets in executive function, attention, and memory research to determine whether this approach systematically reveals hidden effects. Monte Carlo simulations could establish optimal influence detection thresholds for different sample sizes and effect size distributions. Cross-validation studies could determine whether influence-resistant effects show greater replicability across independent samples, potentially establishing this type of sensitivity analysis as standard practice in behavioral neuroscience.

Extreme Groups Design Optimization. The current study's quartile-based extreme groups approach proved superior to traditional correlational methods for detecting trait-state relationships. Systematic comparison studies could test alternative grouping strategies (quintiles, deciles, median splits) across different construct domains to establish optimal extreme groups methodologies. Power analysis simulations could determine minimum sample sizes required for reliable extreme groups detection across different effect size ranges, providing methodological guidance for future endophenotype research.

Comprehensive Generic Model Validation Study

Arguably, the most fulsome validation of Framework B deep decomposed endophenotypes requires implementation of the comprehensive multi-modal research design outlined in Chapter 2's generic model, now enhanced by the theoretical and empirical advances from this study. One approach can revive candidate gene studies and the currently frozen *Genes* unit of measure of the RDoC. By way of example, an implementation of the generic model from Chapter 2 can comprise a full candidate gene study using DRD4-7R VNTR polymorphism grouping, for example, where participants would be genotyped and divided into treatment groups (DRD4-7R VNTR genotype positive) and control groups (genotype negative), then administered the complete assessment battery (e.g., BIS-11, MMPI-IV, MCMI-IV pre-behavioral measurement) and then laboratory behavioral measures while undergoing simultaneous neuroimaging (e.g., fMRI and/or EEG/ERP or NIRS). Framework B discoveries now arguably provide the precise behavioral anchors necessary for implementing this ambitious design with potentially superior methodological sophistication.

Enhanced Generic Model Design. Developing the example above, the comprehensive study would recruit approximately 200-300 participants stratified by DRD4-7R genotype status, with equal representation across the four behavioral phenotypes (ADHD, ASD, schizophrenia, BPD) examined in the current study. All participants would complete the validated assessment battery: BIS-11 (with Factor I motor impulsivity as primary predictor), MMPI-2-RF and MCMI-IV for comprehensive clinical characterization, and the three laboratory behavioral instruments (WCST, GNG, SST) focusing on Framework B deep decomposed endophenotypes (components, features).

Behavioral Phenotype-Specific Assessment Batteries. Critical studies should include matched samples across all four behavioral phenotypes of this study assessed under identical conditions to establish whether Framework B patterns can achieve differential diagnosis where traditional approaches fail. ADHD-focused studies should incorporate attention-specific instruments (CPT-3, TOVA) and subtype-specific rating scales (Conners, ADHD-RS-5). ASD-focused studies should include diagnostic gold standards (ADOS-2, ADI-R) and repetitive behavior measures (RBS-R). Schizophrenia-focused studies should incorporate symptom assessment (PANSS, SIPS for prodromal cases) and cognitive batteries (MCCB). BPD-focused studies should incorporate specialized instruments including PAI-BOR, DIB-R, PNI, PPI-R, STAXI-2, and instruments sensitive to spectrum presentations (SCID-5, Structured Interview for Schizotypy-Revised, Psychosis Proneness Scales) to capture the full range of presentations along the proposed BPD-schizophrenia spectrum. Stress-induction (perturbational) protocols during behavioral assessment would test whether Framework B discrimination patterns change under ecological stress conditions that trigger BPD symptom activation.

Simultaneous EEG/ERP with eLORETA spatiotemporal computational neuroimaging recording during laboratory behavioral task performance would provide millisecond-resolution mapping of the predicted mesocortical versus mesolimbic circuit engagement patterns, while complementary structural and functional MRI (fMRI) or diffusion tensor imaging (DTI) could validate spatial predictions about prefrontal cortical dysfunction and dopaminergic pathway integrity. Participants would complete assessments using all four framework combinations to enable direct comparison of genotype-endophenotype relationships across different measurement approaches, testing whether genetic variants show framework-specific associations.

Framework B Integration Advantages. The current study's discoveries provide multiple advantages for the generic model's implementation. Framework B components (features) serve as validated dependent variables with established discriminant validity, arguably eliminating the measurement uncertainty that has plagued previous candidate gene studies. The GNG-impulsivity/SST-compulsivity theoretical framework generates specific hypotheses about differential DRD4-7R VNTR associations, with predictions that the polymorphism should show stronger associations with GNG_CE (impulsivity control) than SST_OE (attention bridge mechanisms). Cook's distance leverage-residual (influence) sensitivity analysis protocols would ensure that influential outliers do not mask genuine genotype-phenotype relationships, addressing a critical methodological gap in previous candidate gene research described in Chapter 2.

Multi-Modal Statistical Integration. The comprehensive dataset would enable sophisticated analytical approaches including structural equation modeling linking genotype → neuroimaging → Framework B endophenotypes → clinical phenotypes, machine learning (ML) classification algorithms using integrated features for diagnostic prediction, and network analysis revealing dynamic relationships between genetic liability, neural network circuit function, and behavioral control mechanisms. Polygenic risk scores (PRS) for each behavioral phenotype could supplement single-gene analysis, testing whether Framework B deep decomposed endophenotypes mediate polygenic effects on clinical presentations.

Validation of Digital Twin Feature Sets. This comprehensive generic model study would also provide the multi-modal validation data necessary for developing sophisticated digital twin neurocomputational models of behavioral phenotypes. For example, Framework B behavioral profiles, combined with genetic, neuroimaging, and clinical data would create the

high-dimensional feature sets required for reliable AI model supervised training. The validated endophenotype-genotype-neural circuit relationships would enable mechanistically grounded digital twins that capture both reductionist component relationships and emergent system properties, supporting the NDST-informed neurocomputational approaches outlined in the following section.

Clinical Translation Pathway. Success of the generic model study would establish Framework B profiling as a translational bridge between research discoveries and clinical applications. Validated genotype-endophenotype relationships could guide personalized intervention selection, while neuroimaging-endophenotype correlations could inform treatment monitoring approaches. The multi-modal assessment protocol itself could be adapted for clinical settings, providing objective endophenotype-based diagnostic support that transcends traditional categorical boundaries.

Behavioral Phenotype-Specific Translation Priorities. The successful differentiation of BPD from schizophrenia using Framework B profiling would represent a transformative advance for psychiatric practice, potentially resolving one of the field's most persistent diagnostic challenges. This could establish objective, neurocognitive criteria for differential diagnosis where purely symptom-based approaches have failed, fundamentally improving treatment selection and patient outcomes—preventing BPD patients from receiving antipsychotic-focused treatment and schizophrenia patients from receiving DBT-focused interventions. Similarly, ADHD subtype differentiation could inform stimulant versus non-stimulant medication selection, while ASD severity profiling could guide individualized behavioral intervention intensity.

This comprehensive validation generic model study represents the natural culmination of the research program initiated by the current study, establishing the complete empirical

foundation necessary for advanced neurocomputational applications. The validated Framework B endophenotypes, when combined with genetic, neuroimaging, and clinical assessment data from the generic model design, would provide the high-dimensional, multi-modal feature sets required for sophisticated digital twin neurocomputational model development. These integrated datasets would enable the transition from reductionist endophenotype identification to emergent neurocomputational modeling approaches that capture both component-level mechanisms and complex system dynamics. The systematic progression from immediate empirical extensions through comprehensive multi-modal validation creates the robust knowledge base necessary for the advanced neurocomputational modeling and digital twin applications discussed in the following section.

Clinical Regulatory and Implementation Pathway. Translation of Framework B (or other Frameworks from this study) profiling into clinical practice requires navigating complex regulatory frameworks for medical devices and clinical assessment tools. Non-AI clinical assessment protocols incorporating Framework B endophenotypes would likely fall under FDA guidance for laboratory developed tests (LDTs) and clinical decision support tools (U.S. Food and Drug Administration, 2022). Multi-site clinical validation studies would need to demonstrate analytical validity, clinical validity, and clinical utility following FDA's framework for evaluating genetic tests and biomarkers (U.S. Food and Drug Administration, 2018). Professional clinical psychology and psychiatry organizations would need to develop practice guidelines for Framework B implementation, potentially requiring updates to clinical training curricula and continuing education requirements. Reimbursement pathways through Centers for Medicare & Medicaid Services (CMS) would necessitate demonstration of clinical utility and cost-effectiveness compared to standard diagnostic approaches (Centers for Medicare &

Medicaid Services, 2021). International implementation would require alignment with corresponding regulatory bodies and professional standards in target markets.

Neurocomputational Applications

This section of Chapter 5 focuses on recommendations for future research for the development of neurocomputational AI applications discussed in Chapter 2, informed by the findings of this study described in detail in Chapter 4. The focus here is Framework B, although Framework A, C, and D can also become the focus in each case, comparatively or individually. The goal of this section is to suggest explicit and detailed AI architectures that can be not only researched and developed for future research applications, but also tested, validated, and practically and clinically deployed in an FDA and other legally regulated environment for application to the behavioral phenotypes of this study.

The progression begins with individual AI model architectures optimized for specific behavioral phenotype characteristics, including Bayesian non-parametric approaches for ADHD's heterogeneous presentations, manifold learning for ASD's dimensional nature, supervised classification for schizophrenia's complexity, and temporal modeling for BPD's dynamic patterns. These individual approaches are then integrated through ensemble digital twin architectures that leverage complementary strengths across multiple modeling paradigms. Given legal requirements for clinical deployment, comprehensive explainable AI (XAI) and regulatory frameworks are essential for meeting FDA Software as Medical Device standards and ensuring transparent, interpretable medical and psychiatric decision support. The progression from reductionist model development to emergent ensemble applications exemplifies the NDST-informed approach discussed in Chapter 2, where precise decomposition of system elements enables sophisticated modeling of their complex interactions while maintaining clinical utility

and regulatory compliance (Durstewitz et al., 2019; Mujica-Parodi & Strey, 2020). Finally, the last section addresses clinical translation and implementation strategies, including workflow integration, clinician training requirements, evidence generation protocols, and current limitations that define future research priorities. The overall progression from further research recommendations to technical development to regulatory compliance and practical implementation provides an outline for the path from basic research to clinical deployment.

The candidate Framework B deep decomposed endophenotypes (NPE + GNG_CE + SST_OE) identified by this study can provide a robust foundation for advanced neurocomputational modeling of behavioral phenotypes through artificial intelligence (AI) applications. As discussed in detail in Chapter 2, neurocomputational models deploy computational algorithms, including machine learning (ML) and deep learning (DL), to solve, interpret, render, or evolve complex mathematical and statistical models that can be descriptive, explanatory, and predictive of neurobiological systems (Anderson, 2014; Sterratt et al., 2024). The successful demonstration by this study that endophenotype decomposition can help resolve trait-state measurement discordance while revealing genuine behavioral control mechanisms creates opportunities for transformative advances in computational psychiatry and precision psychiatric medicine applications.

AI applications in computational and behavioral neuroscience and in computational psychiatry over the past few decades have evolved from simple pattern recognition to sophisticated ensemble methods capable of modeling the complex, multifactorial presentations observed in ADHD, ASD, schizophrenia, and BPD (Bzdok & Meyer-Lindenberg, 2018; Durstewitz et al., 2019). The high comorbidity rates observed in this study (e.g., 55.4% ADHD-ASD overlap, 43% BPD-schizophrenia overlap) exemplify the differential diagnostic challenges

that traditional DSM focused categorical approaches struggle to address, while dimensional endophenotype-based AI models can offer superior discriminative capacity (Marquand et al., 2016; Plana-Ripoll et al., 2019). Framework B components can serve as empirically validated selected input features that bridge the gap between laboratory behavioral measurement and computational modeling, addressing the fundamental principle established in Chapter 2 that “better inputs result in better outputs” in neurocomputational applications.

Theoretical Foundation and Framework B Integration: From Endophenotype Decomposition Feature Selection to Feature Engineering

The transformation from deep decomposed behavioral endophenotypes to computational input features requires mathematical preprocessing that preserves the discriminative properties identified through this study's empirical validation while enabling optimal AI model performance. Framework B components (NPE + GNG_CE + SST_OE) represent empirically validated features that achieved the most optimal power-parsimony combination, partial $\eta^2 = .040$, among multiple statistically significant framework combinations (e.g., Framework A [Optimal Performance], with 5 deep endophenotypes, had the largest effect size of all four frameworks, partial $\eta^2 = .046$) through systematic MANOVA and sensitivity analyses. While computational efficiency often favors dimensional reduction, the endophenotype decomposition approach of this study demonstrates that preserving discriminative dimensionality can enhance, rather than compromise, model accuracy when components capture non-redundant causal mechanisms. NPE captures prefrontal cortical dysfunction through cognitive flexibility deficits, GNG_CE measures prepotent response inhibition through motor control failures, and SST_OE reflects attention regulation deficits that bridge impulsivity and compulsivity mechanisms. This validated combination provides the empirical foundation necessary for reliable machine learning

applications (Chen et al., 2020; Mihalik et al., 2020). It also addresses the fundamental principle that enhanced input quality produces improved model performance while preserving essential discriminative information rather than collapsing complex behavioral control mechanisms into computationally convenient but theoretically impoverished representations. With robust and empirically validated feature selection complete, feature engineering presents the next step.

Feature engineering for AI applications would begin with normalization and scaling to ensure equivalent contribution across the three Framework B components, given their different measurement scales and distributions. The standard normalization transformation can be expressed as

$$\mathbf{z}_i = \frac{(x_i - \boldsymbol{\mu})}{\boldsymbol{\sigma}}$$

where $\mathbf{z}_i$ represents the normalized feature vector for participant i , x_i represents the raw Framework B scores, $\boldsymbol{\mu}$ represents the feature mean vector, and $\boldsymbol{\sigma}$ represents the feature standard deviation vector (Hastie et al., 2019). This transformation would ensure that NPE (cognitive flexibility), GNG_CE (motor inhibition), and SST_OE (attention regulation) contribute proportionally to model training rather than being dominated by scale differences.

Information-theoretic measures could provide additional insight into feature importance and redundancy within the Framework B combination. Mutual information between features can be calculated as

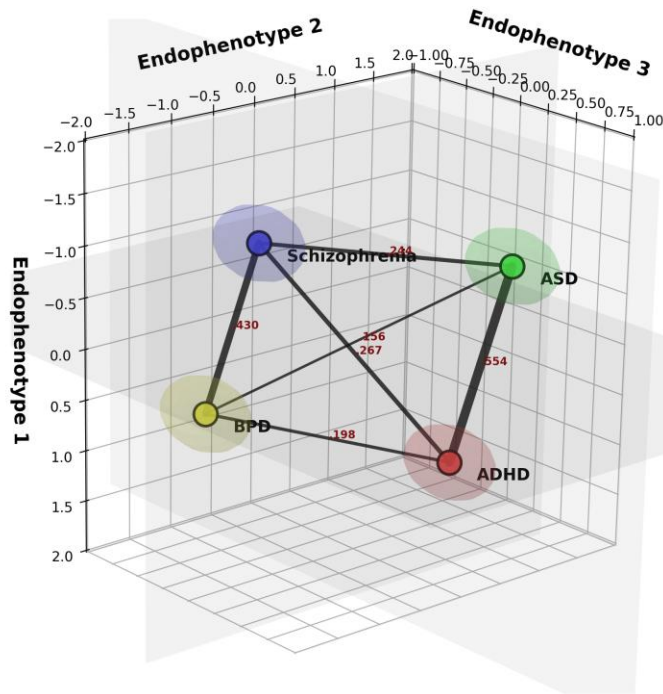
$$I(X; Y) = \sum_{x \in X} \sum_{y \in Y} p(x, y) \log_2 \left(\frac{P(x, y)}{(p(x)p(y))} \right)$$

where $I(X; Y)$ represents the mutual information between Framework B components X and Y , $p(x, y)$ represents the joint probability distribution (joint probability mass function), and $p(x), p(y)$

represent the marginal probability distributions (marginal probability mass functions of x and y ; Cover & Thomas, 2020). This analysis would confirm that Framework B components provide complementary rather than redundant information, supporting their integration in ensemble models discussed later in this section.

The feature space dimensionality of Framework B ($d = 3$) would provide an optimal balance between model complexity and interpretability for clinical applications. As established in machine learning theory and discussed in Chapter 2, the curse of dimensionality becomes problematic when the number of features approaches or exceeds the number of observations (high dimensional feature space), but Framework B's low dimensionality relative to the study's robust sample size ($n = 480$) would ensure stable model training across all proposed architectures (Hastie et al., 2019; James et al., 2021).

NDST-Informed Mathematical Framework. The phase space topology of Framework B components can be conceptualized as a three-dimensional manifold (a term from mathematical topology, Figure 64) where each dimension represents one deep endophenotype component, and behavioral phenotypes would occupy distinct regions within this space with their spatial coordinates determined using multidimensional scaling (MDS) based on comorbidity weighting factors (Gachkooban1 et al., 2024). As described previously and in Chapter 4, ADHD-ASD and BPD-schizophrenia had the strongest comorbidity rates from this study, as was also suggested in Chapter 2 (e.g., see Chapter 2 section on BPD-Schizophrenia relationship). From a dynamical systems perspective, behavioral phenotype classification would become a problem of identifying decision boundaries that optimally separate these regions while accounting for the natural variability observed within each behavioral phenotype (Ott, 2002; Strogatz, 2018).

Figure 64*3D Manifold of Behavioral Phenotype Phase Space*

Note: Dynamic 3D manifold visualizing behavioral phenotypes as regions in a continuous phase space derived from comorbidity data from this study and Framework B using Multidimensional Scaling (MDS). Each axis represents a deep endophenotype component (i.e., WCST_NPE, GNG_CE, SST_OE), and the spatial relationships reflect empirical comorbidity patterns. The manifold shows how behavioral phenotypes cluster in theoretical endophenotype space, with overlapping regions indicating comorbidity potential. The closer two behavioral phenotypes appear (the thicker the lines), the higher their empirical comorbidity rate. High comorbidity corresponds to closer proximity in the manifold space. Gray surfaces represent probabilistic classification boundaries between phenotype regions. Computer code written in Python 3.13.5 with *numpy*, *matplotlib*, *scipy*, and *seaborn* packages installed and run using IDLE python shell

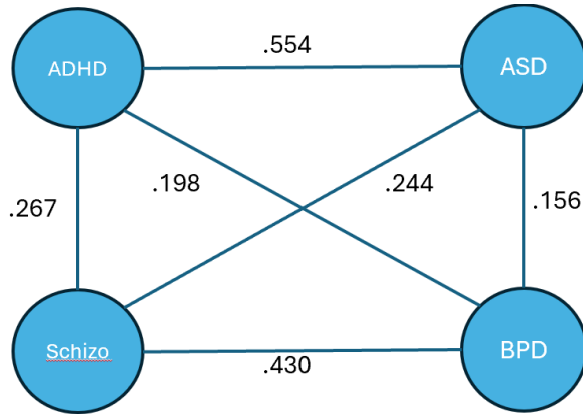
3.13.5 with dynamic generative visualization, APA 7 format data structure generator, and .png capture (Python code available from author).

The Framework B phase space can be mathematically represented as

$$\Phi: \mathbb{R}^3 \rightarrow BP \quad (42)$$

where Φ represents the mapping function from the three-dimensional Framework B space to the phenotype space $BP = \{\text{ADHD, ASD, Schizophrenia, BPD}\}$, and the optimal decision boundaries would be determined through AI model training (Perko, 2013). The high comorbidity rates observed in this study suggest that these behavioral phenotype regions would exhibit significant overlap, requiring sophisticated modeling approaches capable of handling probabilistic rather than deterministic classification.

Graph-theoretic modeling of comorbidity networks provides a basic mathematical structure for understanding behavioral phenotype relationships. The comorbidity network can be represented (Figure 65) as a weighted graph $G = (\mathbf{V}, \mathbf{E}, \mathbf{W})$ where $\mathbf{V}$ represents the set of behavioral phenotype vertices $\{\text{ADHD, ASD, Schizophrenia, BPD}\}$, $\mathbf{E}$ represents the edges connecting comorbid behavioral phenotypes, and $\mathbf{W}$ represents the weight matrix containing comorbidity percentages observed in this study (Newman, 2018).

Figure 65*Weighted Comorbidity Network*

Note: The edges (**E**) show the weights (**W**) between the vertices (**V**) representing the four behavioral phenotypes. Comorbidity rates (weights) are based on self-reports of clinical diagnosis ($n = 6,603$ for participant sample, $n = 954$ for study sample, $n = 480$ for study group) described in Chapter 4 (Table 13).

The adjacency matrix **A** for this comorbidity network is (43)

$$\mathbf{A} = \begin{bmatrix} 0 & .554 & .267 & .198 \\ .554 & 0 & .244 & .156 \\ .267 & .244 & 0 & .430 \\ .198 & .156 & .430 & 0 \end{bmatrix}$$

where matrix elements represent the observed comorbidity percentages from Chapter 4 (.554 = 55.4% ADHD-ASD overlap, .430 = 43.0% BPD-schizophrenia overlap, .156 = 15.6% ASD-BPD overlap, .267 = 26.7% ADHD-schizophrenia overlap, .244 = 24.4% ASD-schizophrenia overlap, .198 = 19.8% ADHD-BPD overlap). This mathematical representation would enable graph neural network (GNN) approaches to explicitly model phenotype relationships during classification tasks.

The temporal dynamics of behavioral phenotypes, particularly relevant for BPD's stress-triggered presentations, could be modeled using stochastic differential equations that capture the phase transitions between stable and dysregulated states. A simplified representation of BPD state dynamics can be expressed as

(44)

$$\frac{d\mathbf{x}}{dt} = f(\mathbf{x}, u) + \sigma(\mathbf{x})\xi(t)$$

where $\mathbf{x}$ represents the current behavioral state vector (incorporating Framework B components), $f(\mathbf{x}, u)$ represents the deterministic component of state evolution with stress input u , $\sigma(\mathbf{x})$ represents the state-dependent noise intensity, and $\xi(t)$ represents Gaussian white noise (Evans, 2012; Øksendal, 2013). This mathematical framework would provide the theoretical foundation for Hidden Markov Model (HMM) applications in BPD state transition modeling.

Individual Model Architectures

The following individual model architectures represent distinct AI approaches optimized for specific behavioral phenotypes based on their unique symptomatic presentation dynamics and clinical requirements. Each architecture leverages Framework B components as validated input features while employing different mathematical frameworks to address behavioral phenotype-specific challenges: infinite mixture modeling using Dirichlet processes for ADHD's heterogeneous subtypes, manifold learning for ASD's dimensional presentations, supervised classification for schizophrenia's severity and complexity, and temporal state modeling for BPD's dynamic emotional regulation patterns. These architectures provide the foundational components for subsequent ensemble integration approaches that can leverage their complementary strengths for comprehensive behavioral phenotype modeling. Although the focus is on Framework B due to its previously discussed superior power-parsimony optimized performance and computational

efficiency, Frameworks A, C, and D can also serve as foundational feature input spaces, comparatively or individually.

Bayesian Non-Parametric Dirichlet Gaussian Mixture Models for ADHD Subtyping.

ADHD presents unique challenges for subtype classification due to the heterogeneity within DSM-5 categories and the high comorbidity observed with other behavioral phenotypes (37-85% with ASD as noted in Chapter 2). Traditional approaches assume fixed numbers of subtypes (parametric structure), but Bayesian non-parametric Dirichlet Gaussian Mixture Models (DGMMs) could enable automatic discovery of natural clustering patterns without pre-specifying cluster numbers (nonparametric), making them potentially optimal for ADHD's complex presentation patterns (Gershman & Blei, 2012; Teh, 2010).

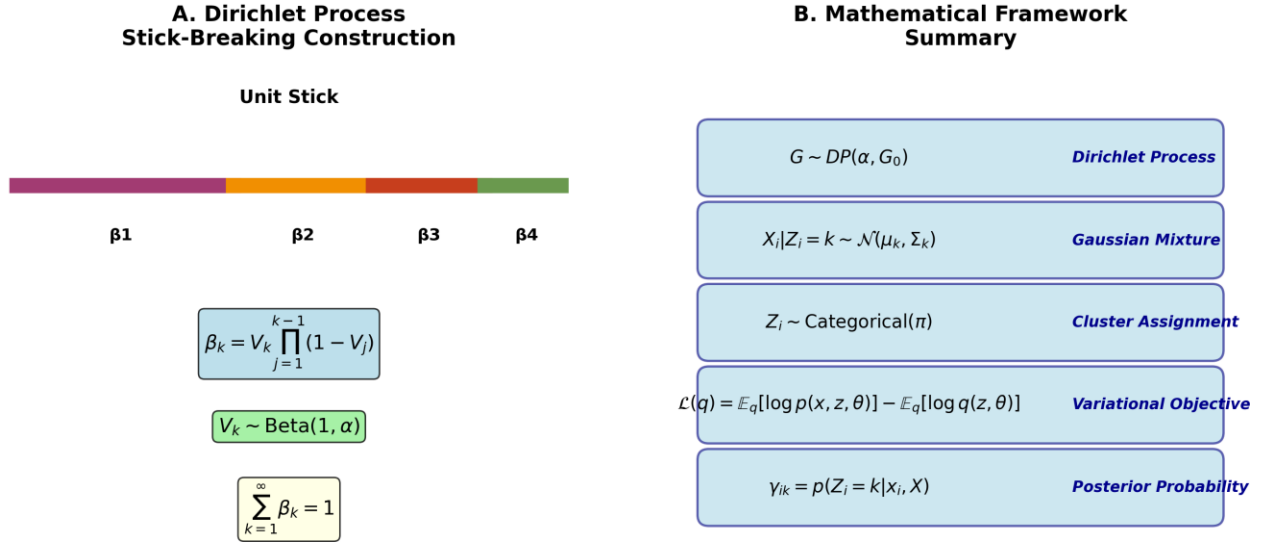
Mathematical Foundation of DGMMs. The Dirichlet Process (DP) would provide the mathematical framework for infinite mixture modeling through the stick-breaking construction (Sethuraman, 1994). A Dirichlet Process can be formally defined as

$$G \sim DP(\alpha, G_0) \quad (45)$$

where G represents a random probability measure, α represents the concentration parameter controlling cluster formation propensity, and G_0 represents the base measure defining the Bayesian prior distribution over cluster parameters (Ferguson, 1973; Sethuraman, 1994). The stick-breaking representation makes this construction explicit

$$\beta_k = V_k \prod_{j=1}^{k-1} (1 - V_j) V_k \sim \text{Beta}(1, \alpha) \pi_k = \beta_k \quad (46)$$

where β_k represents the weights for each cluster k , V_k represents the stick-breaking variables following a Beta distribution, and π_k represents the mixture weights ensuring $\sum \pi_k = 1$ (Pitman, 2006). Figure 66 summarizes the stick breaking and mathematical framework.

Figure 66*Dirichlet Gaussian Mixture Model Theoretical Framework for ADHD Subtyping*

Note: Dirichlet Process stick-breaking construction (Panel A) enables automatic discovery of ADHD subtypes without preset categories through infinite mixture modeling. Mathematical framework summary (Panel B) presents key equations including Dirichlet Process formulation, Gaussian mixture components, and variational objective function for tractable Bayesian inference.

For ADHD subtyping using Framework B features, the model would assume that each participant's feature vector $\mathbf{x}_i = [\text{NPE}, \text{GNG\_CE}, \text{SST\_OE}]$ is generated from one of potentially infinite Gaussian clusters

$$Z_i \sim \text{Categorical}(\pi) \mathbf{X}_i | Z_i = k \sim \mathcal{N}(\boldsymbol{\mu}_k, \boldsymbol{\Sigma}_k) \mu_k \sim \mathcal{N}(m, \frac{S}{\kappa}) \boldsymbol{\Sigma}_k \sim \text{InvWishart}(v, \Psi) \quad (47)$$

where z_i represents the cluster assignment for participant i , μ_k and Σ_k represent the mean vector and covariance matrix for cluster k , and the hyperparameters m , S , κ , v , Ψ would define the prior distributions (Neal, 2000; Rasmussen, 2000). The Inverse Wishart distribution is the conjugate

Bayesian prior for the covariance matrix of a multivariate Gaussian distribution, enabling computationally efficient Bayesian inference (Gelman et al., 2013).

Variational Inference Implementation. Exact inference in DGMMs is intractable, requiring approximate methods such as variational inference. The variational objective function to be maximized is

$$\mathcal{L}(q) = \mathbb{E}_q[\log p(x, z, \theta)] - \mathbb{E}_q[\log q(z, \theta)] \quad (48)$$

where $q(z, \theta)$ represents the variational approximation to the true Bayesian posterior $p(z, \theta | x)$, and the expectation is taken with respect to the variational distribution (Blei et al., 2017; Jordan et al., 1999). This optimization would enable automatic determination of the optimal number of ADHD subtypes based on the data rather than imposing DSM-5's three-category structure (Figure 69.A).

Architecture Specifications of DGMM for ADHD. The DGMM implementation for ADHD subtyping can incorporate Framework B features as primary inputs while allowing integration of additional demographic and genetic features for enhanced discrimination. The concentration parameter α would be treated as a hyperparameter with a Gamma Bayesian prior $\alpha \sim \text{Gamma}(a, b)$ to enable automatic adaptation to the data's clustering structure (Escobar & West, 1995). Initial studies suggest $a = 1, b = 1$ would provide reasonable non-informative Bayesian priors, but optimization should be performed on validation data.

The model output would provide Bayesian posterior probability distributions over cluster assignments for each participant

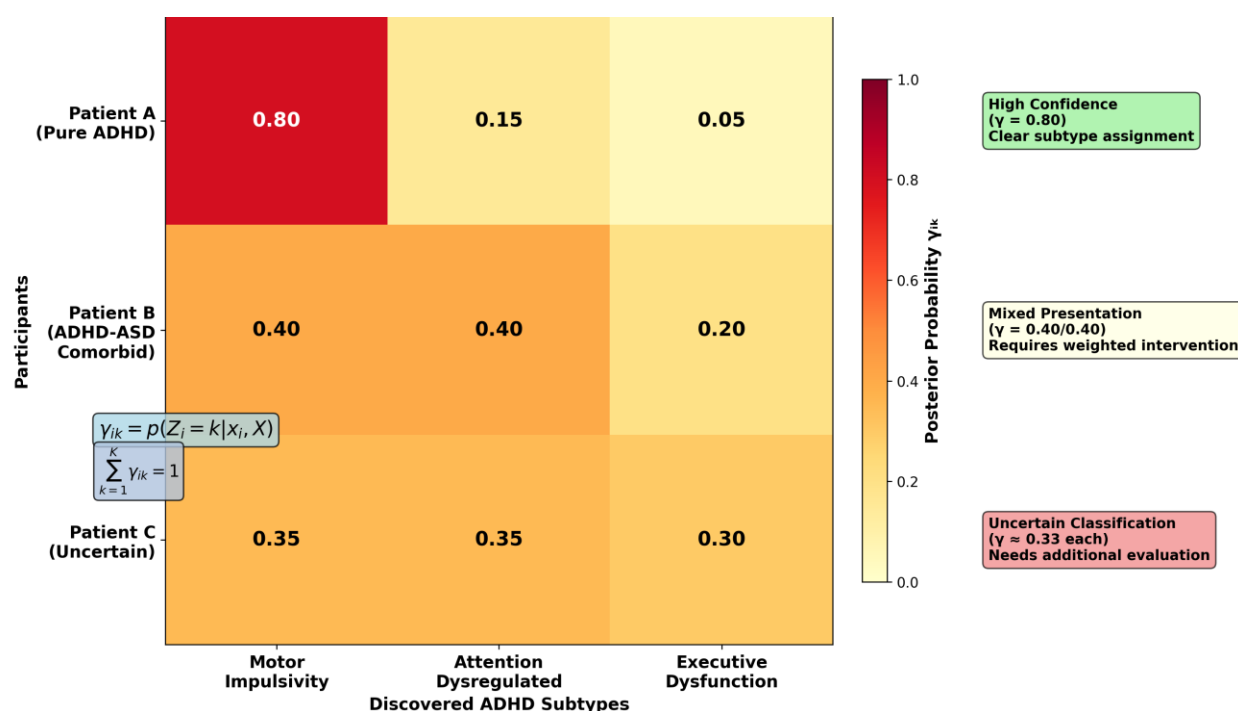
$$p(z_i = k | x_i, X) = \gamma_{ik} \quad (49)$$

where γ_{ik} represents the responsibility of cluster k for participant i , and $\sum_k \gamma_{ik} = 1$ (Bishop, 2006). This probabilistic output (Figure 67) would enable the uncertainty quantification that is essential

for clinical applications, providing confidence measures for subtype assignments rather than hard categorical decisions.

Figure 67

Probabilistic Subtype Assignment for ADHD-ASD Comorbidity Management



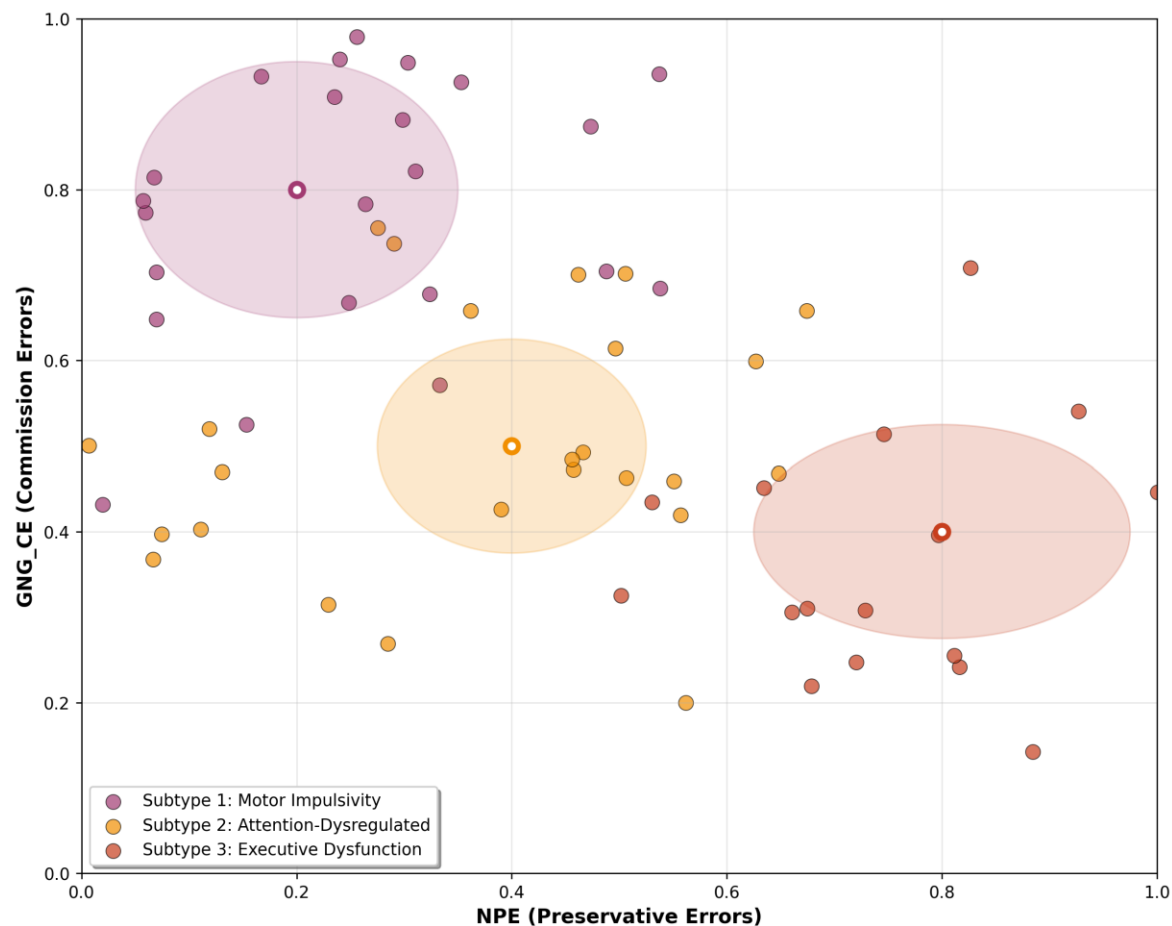
Note: Probabilistic subtype assignments demonstrate DGMM capability to handle diagnostic uncertainty and comorbidity. Patient A shows clear motor impulsivity subtype ($\gamma = 0.80$), Patient B exhibits mixed ADHD-ASD presentation requiring weighted intervention approaches ($\gamma = 0.40/0.40$), and Patient C represents uncertain classification necessitating additional evaluation.

Clinical Applications of DGMM for ADHD. The DGMM approach could arguably address ADHD's diagnostic challenges by discovering natural subtypes that may not correspond to DSM-5 categories but represent genuine neurobiological distinctions. Preliminary applications suggest the model might identify subtypes characterized by: (a) pure motor impulsivity (high

GNG_CE, low SST_OE), (b) attention-dysregulated (high SST_OE, moderate GNG_CE), and (c) executive dysfunction (high NPE, moderate other components) patterns (Marquand et al., 2016; van Hulst et al., 2015). Figure 68 illustrates the subtype clusters.

Figure 68

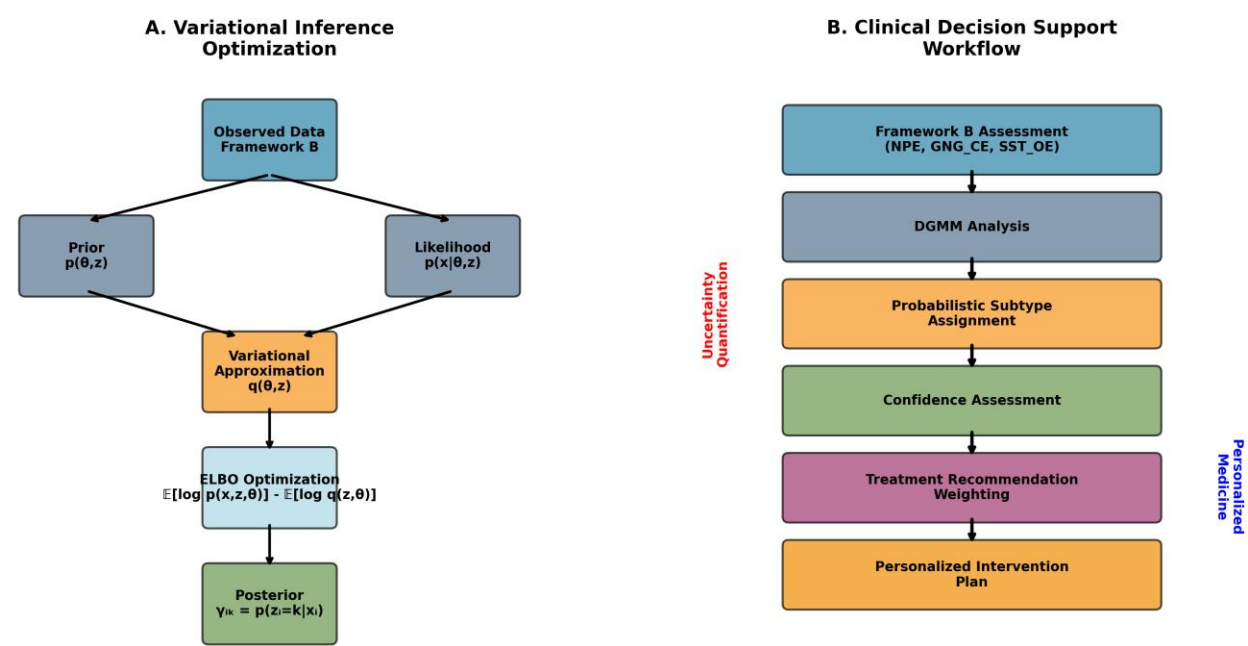
Framework B Deep Endophenotype Clustering in ADHD Behavioral Subtypes



Note: Framework B deep endophenotypes (NPE, GNG_CE, SST_OE) cluster naturally into three ADHD behavioral subtypes: motor impulsivity (high commission errors, low stop-signal errors), attention-dysregulated (high stop-signal errors, moderate commission errors), and executive dysfunction (high preservative errors, moderate other components). Ellipses represent 95% confidence regions for discovered clusters.

The probabilistic nature of DGMM outputs would enable handling of the 55.4% ADHD-ASD comorbidity observed in this study, for example, by allowing participants to have partial membership in multiple clusters, potentially revealing transitional behavioral phenotypes that bridge diagnostic categories. This capability could be particularly valuable for personalized intervention planning (Figure 69.B), where treatment protocols can be weighted according to subtype probability distributions rather than assuming categorical membership (Dinga et al., 2019; Nunes et al., 2020).

Figure 69
DGMM Implementation: Variational Inference and Clinical Decision Support Workflow



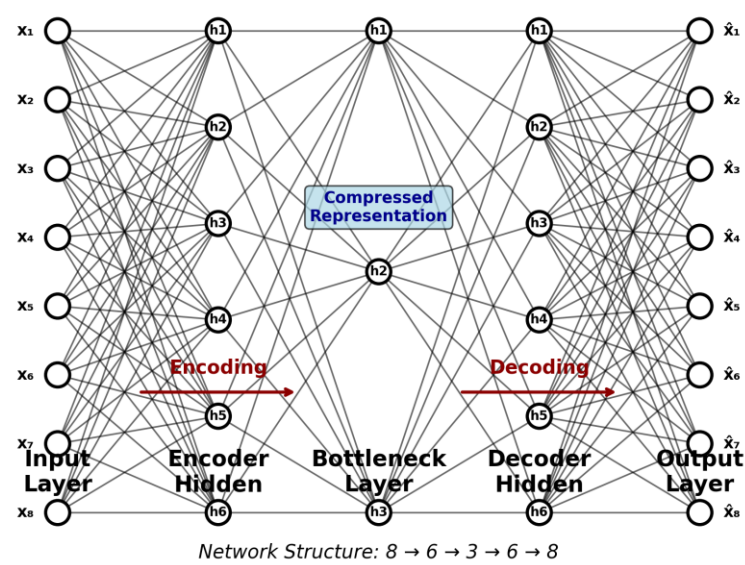
Note: Variational inference optimization (Panel A) maximizes evidence lower bound through iterative approximation of posterior distributions. Clinical decision support workflow (Panel B) integrates uncertainty quantification for personalized intervention planning, enabling treatment recommendation weighting based on probabilistic subtype assignments.

Overparametrized Autoencoders for ASD Behavioral Phenotype Discovery. Autism Spectrum Disorder (ASD) presents unique challenges for neurocomputational modeling due to its dimensional nature, with severity levels ranging from minimal support needs (often for Asperger type presentations) to requiring very substantial support, and heterogeneous presentations spanning social communication deficits and restricted repetitive (perseverative) behaviors (American Psychiatric Association, 2022). Overparametrized autoencoders could provide an optimal architecture for discovering latent dimensional structures within ASD presentations while maintaining interpretability for clinical applications (Charte et al., 2018; Durstewitz et al., 2019).

Mathematical Foundation of OAEs. An autoencoder (Figure 70) is a feed forward symmetrical multi-layer neural network that consists of an encoder function f that maps input features to a latent dimensionally reduced representation and a decoder function g that reconstructs the original input from the latent space (Charte et al., 2018).

Figure 70

Basic Autoencoder Architecture



For Framework B features $x \in \mathbb{R}^3$, the encoder transformation can be expressed as

$$z = f(x) = \sigma(\mathbf{W}_e x + \mathbf{b}_e) \quad (50)$$

where $z \in \mathbb{R}^d$ represents the latent representation with $d \ll 3$ for traditional autoencoders, $\mathbf{W}_e$ represents the encoder weight matrix, $\mathbf{b}_e$ represents the encoder bias vector, and σ represents the activation function (typically ReLU [rectilinear unit] or tanh; Goodfellow et al., 2016; Hinton & Salakhutdinov, 2006).

The decoder function would reconstruct the input as

$$\hat{x} = g(z) = \sigma'(\mathbf{W}^d z + \mathbf{b}^d) \quad (51)$$

where $\hat{x}$ represents the reconstructed Framework B features, $\mathbf{W}^d$ represents the decoder weight matrix, $\mathbf{b}^d$ represents the decoder bias vector, and σ' represents the decoder activation function (often linear for continuous outputs; Bengio, 2009; Vincent et al., 2008).

Overparameterization Strategy. Contrary to traditional autoencoders that use computationally optimizing dimensionality reduction ($d < \text{input\_dim}$), overparametrized autoencoders would employ expansion ratios of approximately 10:1, creating latent spaces with $d = 30\text{-}50$ dimensions for the 3-dimensional Framework B input. This counterintuitive overparameterization could enable the model to learn rich, distributed representations that capture subtle behavioral phenotypic variations within the ASD spectrum (Arpit et al., 2017; Zhang et al., 2021).

The loss function would combine reconstruction error with regularization (as a penalty function) to prevent overfitting (the intuitive outcome of overparameterization) despite overparameterization

$$L = L_{recons} + \lambda \Omega(W) \quad (52)$$

where the reconstruction loss is

$$L_{recons} = \left(\frac{1}{n}\right) \sum_{i=1}^n \|x_i - \hat{x}_i\|^2 \quad (53)$$

and the regularization term $\Omega(W)$ would typically employ L1 or L2 regularization penalties

$$\Omega(W) = \alpha_1 \|W\|_1 + \alpha_2 \|W\|_2^2 \quad (54)$$

where λ , α_1 , and α_2 represent regularization hyperparameters controlling the trade-off between reconstruction accuracy and model complexity (Tibshirani, 1996; Zou & Hastie, 2005).

Manifold Learning and Latent Space Interpretation. The overparametrized latent space could be conceptualized as a learned mathematical manifold M embedded in $\mathbb{R}^d$ where ASD behavioral phenotypes would occupy continuous regions rather than discrete clusters. Local linear embedding principles suggest that nearby points in the latent space would correspond to similar ASD presentations, enabling interpolation between behavioral phenotypes and discovery of transitional states (Roweis & Saul, 2000; Tenenbaum et al., 2000).

The latent space geometry could be analyzed through traditional principal component analysis (PCA) of the learned representations

$$\mathbf{Z} = \mathbf{U}\mathbf{\Sigma}\mathbf{V}^T \quad (55)$$

where $\mathbf{Z}$ represents the matrix of latent representations, $\mathbf{U}$ and $\mathbf{V}$ represent orthogonal matrices of left and right singular vectors, and $\mathbf{\Sigma}$ represents the diagonal matrix of singular values (Jolliffe,

2002). The principal components would reveal the primary axes of variation within ASD presentations, potentially corresponding to severity gradations and subtype distinctions.

Architecture Specifications for OAE for ASD. The overparametrized autoencoder architecture for ASD would employ a symmetric encoder-decoder structure with multiple hidden layers to capture hierarchical feature representations (56)

Encoder: [3] → [128] → [64] → [32] → [latent_dim = 40]

Decoder: [40] → [32] → [64] → [128] → [3]

Each hidden layer would employ ReLU activation with batch normalization and dropout regularization (dropout rate = .2) to prevent overfitting (Ioffe & Szegedy, 2015; Srivastava et al., 2014). The expansion ratio of approximately 13:1 (40 latent dimensions for 3 input dimensions) would enable rich representation learning while maintaining computational efficiency.

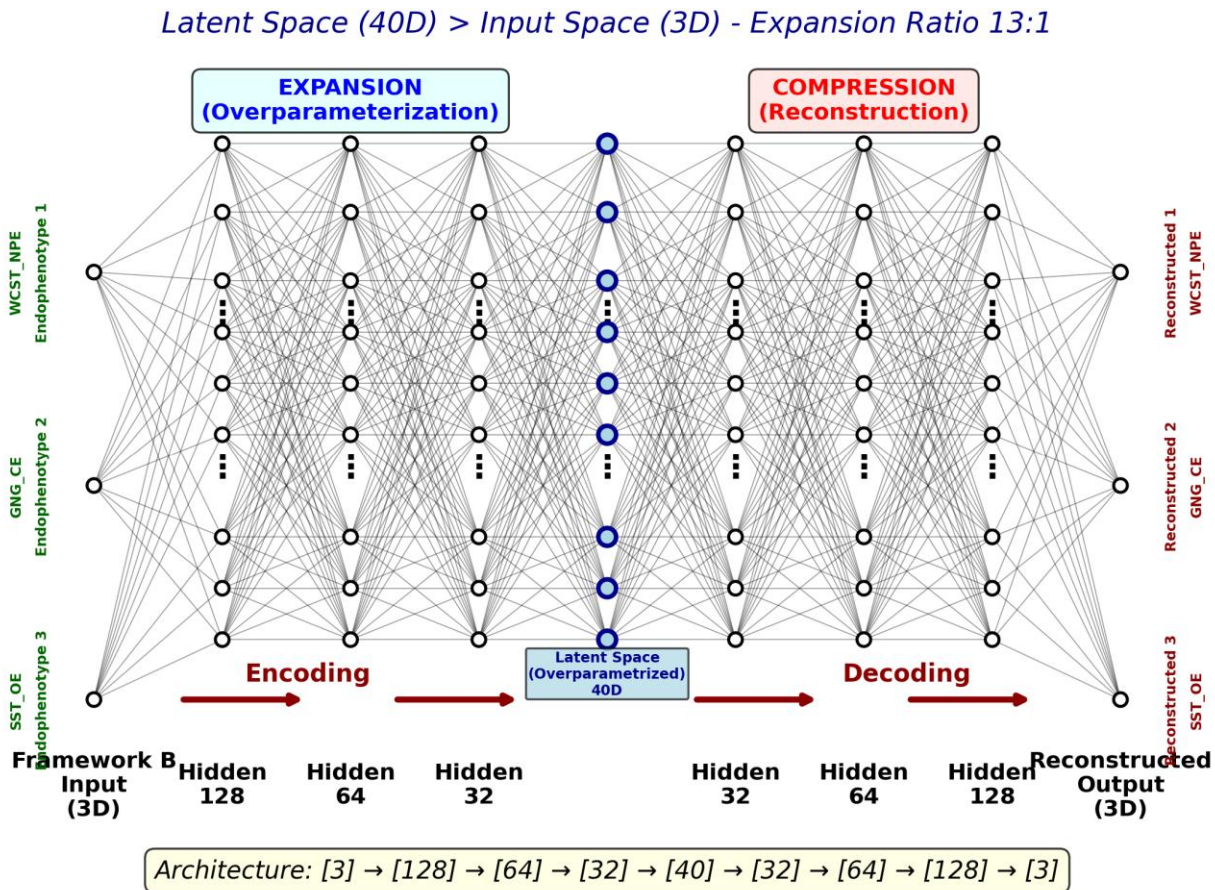
Training could employ the Adam first-order gradient-based stochastic objective function optimizer with adaptive learning rate scheduling (57)

$$\theta_{t+1} = \theta_t - \frac{\alpha \hat{m}_t}{\sqrt{\hat{v}_t + \epsilon}}$$

where θ represents model parameters, α represents the learning rate, $\hat{m}_t$ and $\hat{v}_t$ represent bias-corrected first and second moment estimates, and ϵ represents a small constant for numerical stability (Kingma & Ba, 2014). Figure 71 shows the above specified OAE.

Figure 71

Overparameterized Autoencoder for ASD Framework B



Clinical Applications of OAE for ASD. The overparametrized autoencoder in Figure 72 could provide several clinical applications for ASD assessment and intervention planning. Reconstruction error analysis might enable anomaly detection for identifying atypical ASD presentations that may require specialized assessment or represent novel behavioral phenotypic variants (An & Cho, 2015; Chalapathy & Chawla, 2019). High reconstruction error would indicate that a participant's Framework B profile, for example, deviates significantly from learned ASD patterns, potentially suggesting comorbid conditions or measurement artifacts.

Latent space visualization through t-SNE or UMAP dimensionality reduction could enable clinicians to visualize ASD severity gradations and subtype relationships in interpretable 2D projections (McInnes et al., 2018; van der Maaten & Hinton, 2008). This visualization capability would support the dimensional conceptualization of autism spectrum disorders while providing intuitive representations for clinical decision-making.

The learned latent representations could be used for trajectory modeling, where longitudinal assessments would map onto paths through the latent space, enabling prediction of developmental trajectories and intervention outcomes (Fountain et al., 2012; Shephard et al., 2018). This capability could be particularly valuable for early intervention planning and monitoring treatment response over time.

Multi-Layer Perceptron Neural Networks for Schizophrenia Classification. As discussed in Chapter 2, schizophrenia arguably presents the most severe impulsivity and cognitive control deficits among the four behavioral phenotypes examined in this study, with BRI deficits described as “as bad or worse as those with impulse control disorders.” The complexity and severity of schizophrenia presentations, combined with the need for early detection and treatment response prediction discussed in Chapter 2, suggests that Multi-Layer Perceptron Neural Networks (MLPNNs) could be optimal for robust supervised classification with explainable AI capabilities (Bzdok & Meyer-Lindenberg, 2018; Durstewitz et al., 2019).

Mathematical Foundation of MLPNNs. MLPNNs would implement universal approximation through hierarchical feature learning, where each layer learns increasingly abstract representations of the input data. For Framework B inputs $x \in \mathbb{R}^3$, the forward propagation through an L-layer network can be expressed as

$$\mathbf{a}^0 = x \quad \mathbf{z}^l = \mathbf{W}^l \mathbf{a}^{l-1} + \mathbf{b}^l \mathbf{a}^l = \sigma(\mathbf{z}^l) \quad (58)$$

for $l = 1, 2, \dots, L$, where $\mathbf{a}^l$ represents the activation vector at layer l , $\mathbf{W}^l$ represents the weight matrix connecting layers $l-1$ and l , $\mathbf{b}^l$ represents the bias vector at layer l , and σ represents the activation function (Cybenko, 1989; Goodfellow et al., 2016).

The final layer output for schizophrenia classification can employ softmax activation (converting a vector of real numbers $\mathbb{R}$) to produce probability distributions over behavioral phenotype classes (59)

$$p(y = k | x) = \frac{\exp(z_k^L)}{\sum_{j=1}^K \exp(z_j^L)}$$

where $p(y = k | x)$ represents the probability that input x belongs to class k , and K represents the total number of classes (4 for ADHD, ASD, schizophrenia, and BPD classification; Bishop, 2006).

Backpropagation and Gradient Optimization. Training would employ backpropagation (which adjusts a neural network's weights to minimize the difference between predicted and actual outputs by calculating the error at the output and then propagating it backward through the network and adjusting weights in each layer to reduce the error) to compute gradients through the chain rule of calculus. For a loss function $L(\theta)$, the gradient with respect to weights at layer l is (60)

$$\frac{\partial L}{\partial W^1} = \frac{\partial L}{\partial a^1} \cdot \frac{\partial a^1}{\partial z^1} \cdot \frac{\partial z^1}{\partial W^1}$$

where each partial derivative would be computed recursively through the network layers (LeCun et al., 2015; Rumelhart et al., 1986). The cross-entropy loss function for multi-class classification is

(61)

$$L = -\left(\frac{1}{n}\right) \sum_{i=1}^n \sum_{k=1}^K y_{ik} \log(p(y_i = k | x_i))$$

where y_{ik} represents the one-hot encoded (i.e., representing categorical data as binary vectors) true class labels (Goodfellow et al., 2016).

Gradient descent optimization (which seeks to find the local minima of a function to minimize the loss or cost function by iteratively adjusting the parameters of a model in the direction opposite to the gradient of the function being minimized) with momentum would incorporate previous gradient information to accelerate convergence and escape local minima

$$\theta_{t+1} = \theta_t - \alpha \nabla L(\theta_t) + \mu(\theta_t - \theta_{t-1}) \quad (62)$$

where α represents the learning rate, μ represents the momentum coefficient (typically 0.9), and $\nabla L(\theta_t)$ represents the gradient at iteration t (Sutskever et al., 2013).

Architecture Specifications for MLPNN for Schizophrenia. The MLPNN architecture for schizophrenia classification here would employ a deep network structure optimized for Framework B feature discrimination

Input Layer: 3 neurons (NPE, GNG_CE, SST_OE),
 Hidden Layer 1: 128 neurons (ReLU activation),
 Hidden Layer 2: 64 neurons (ReLU activation),
 Hidden Layer 3: 32 neurons (ReLU activation),
 Output Layer: 4 neurons (Softmax activation).

Each hidden layer would incorporate batch normalization (inputwise normalization) to stabilize training and improve convergence

(63)

$$BN(x) = \gamma \cdot \frac{(x - \mu_\beta)}{\sqrt{\sigma_\beta^2 + \varepsilon}} + \beta$$

where μ_β and σ_β^2 represent batch mean and variance, γ and β represent learnable scale and shift parameters, and ε represents a small constant for numerical stability (Ioffe & Szegedy, 2015).

Dropout regularization would prevent overfitting by randomly setting hidden unit activations to zero during training

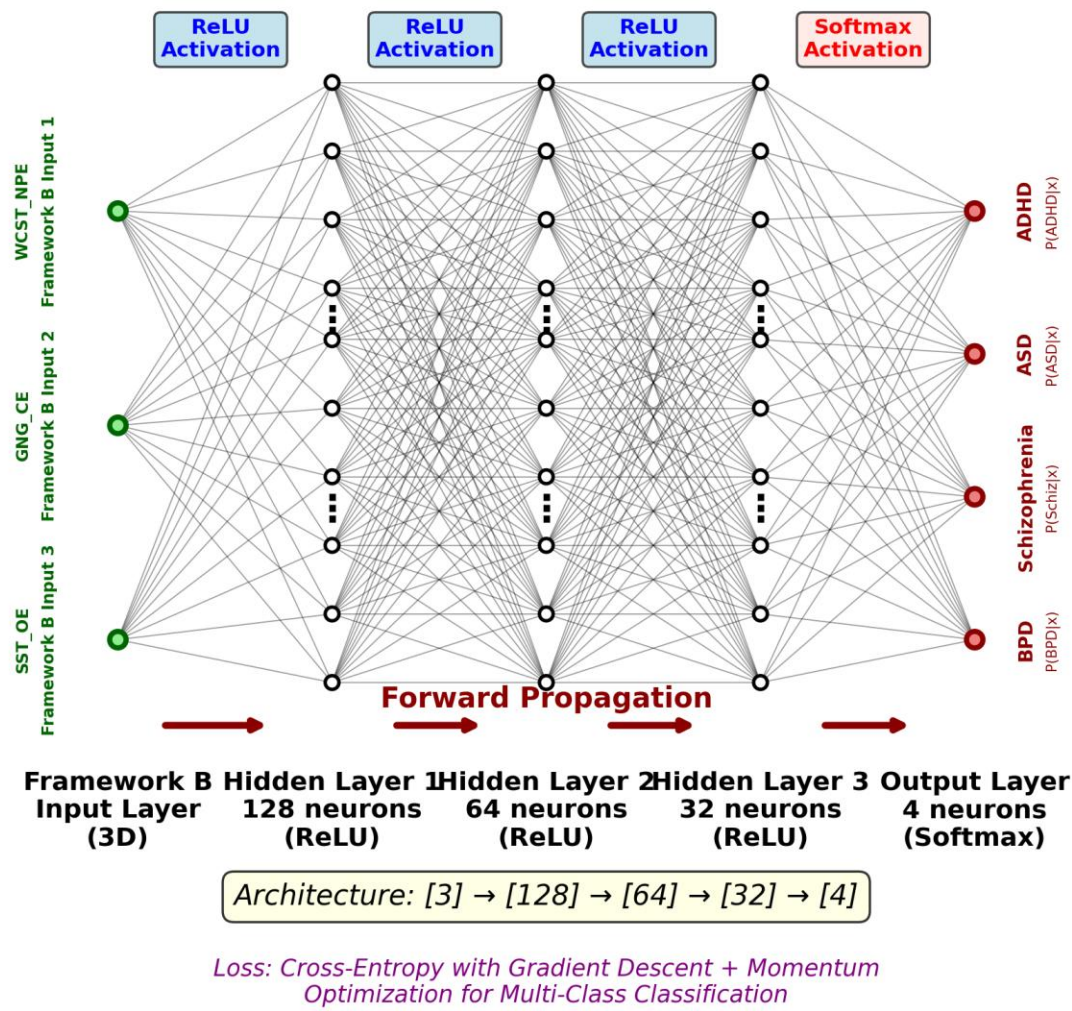
$$r \sim \text{Bernoulli}(p) \quad \tilde{y} = r \odot y \quad (64)$$

where r represents the dropout mask following a Bernoulli probability distribution, p represents the retention probability (typically .7 - .8), y represents the original activations, and $\tilde{y}$ represents the dropped-out activations (Srivastava et al., 2014). The Bernoulli distribution generates binary random variables where each unit has a probability p of being retained and $(1 - p)$ of being dropped during training. Figure 72 shows the above specified MLPNN architecture for schizophrenia differential diagnosis among the behavioral phenotypes of this study.

Figure 72

Multilayer Perceptron Neural Network for Schizophrenia Classification

Supervised Classification: Framework B → Behavioral Phenotype Prediction



Clinical Applications and Explainable AI for MLPNN. The MLPNN approach could address schizophrenia's diagnostic challenges through robust classification while maintaining explainability essential for clinical applications. Early detection capabilities might emerge from the model's ability to identify subtle Framework B patterns that precede full symptom manifestation, potentially enabling intervention during prodromal phases, directly addressing

clinical intervention challenges and improved response from early intervention discussed in Chapter 2 (Fusar-Poli et al., 2013; Lieberman et al., 2018).

Treatment response prediction could leverage the learned feature representations to identify schizophrenia subtypes that respond differentially to antipsychotic medications versus cognitive remediation approaches. The neurocomputational model's probabilistic outputs would enable risk stratification where high-confidence predictions, $p > .8$, proceed with indicated treatments, while low-confidence cases, $p < 0.6$, receive comprehensive evaluation (Dwyer et al., 2018; Koutsouleris et al., 2021).

MLPNNs are black-box AI models in that mechanistic inference is not resolvable (often due to NDST implicated emergent behavior of the model). That is, only inputs and outputs are known, not how outputs are theoretically or practically generated. Clinical tools require an understanding of how outputs are generated mechanistically so inferences can be understood. Thus, MLPNNs require explainability. To facilitate an explainable AI (XAI) solution, SHAP (SHapley Additive exPlanations) values could provide interpretable explanations of individual predictions by computing the marginal contribution of each Framework B component to the final classification decision. The SHAP value for feature i is computed as (65)

$$\varphi_i = \sum_{S \subseteq N \setminus \{i\}} \frac{|S|! (n - |S| - 1)!}{n!} [f(S \cup \{i\}) - f(S)]$$

where φ_i represents the SHAP value for feature i , S represents a subset of features excluding i , n represents the total number of features, and f represents the prediction function (Lundberg & Lee, 2017; Molnar, 2020). These explanations would enable clinicians to understand which specific endophenotype deficits drive schizophrenia classifications, supporting evidence-based treatment planning (SHAP Values are discussed in greater detail later in this chapter).

Hidden Markov Models for BPD State Transition Modeling. As discussed in Chapter 2, borderline personality disorder (BPD) presents unique temporal dynamics characterized by rapid transitions between emotional states (phase transitions), stress-triggered impulsivity activation, and context-dependent symptom expression (Fineberg et al., 2014; Linehan, 2014). Hidden Markov Models (HMMs) could provide optimal mathematical frameworks for modeling these NDST implicating state-dependent processes, where unobservable emotional regulation states would generate observable Framework B patterns through probabilistic emission processes (Bishop, 2006; Rabiner, 1989).

Mathematical Foundation of HMMs. Hidden Markov Models provide mathematical frameworks for modeling temporal behavioral patterns through probabilistic state-dependent processes, particularly suitable for BPD's dynamic emotional regulation cycles (phase transitions). The HMM architecture for BPD applications is characterized by the parameter set $\lambda = (A, B, \pi)$ where A represents state transition probabilities, B represents observation emission probabilities, and π represents initial state distributions (Rabiner, 1989). For BPD emotional regulation modeling, hidden states represent unobservable emotional phases (Stable, Triggered, Dysregulated, Recovery) while observed Framework B measurements serve as state-dependent emissions, enabling inference about underlying emotional regulation processes from behavioral assessment patterns.

The state transition matrix $\mathbf{A} = \{a_{ij}\}$ would define the probability of transitioning from state i to state j

$$a_{ij} = P(q_{t+1} = j \mid q_t = i) \quad (66)$$

where q_t represents the hidden state at time t , and $\sum_j a_{ij} = 1$ for all i (Baum & Petrie, 1966). The transition probabilities could be estimated from longitudinal assessment data or informed by clinical knowledge of BPD state dynamics.

The observation emission probabilities $B = \{b_j(o_t)\}$ would define the likelihood of observing Framework B patterns given hidden emotional states

$$b_j(o_t) = P(o_t | q_t = j) \quad (67)$$

where o_t represents the observed Framework B vector at time t . For continuous observations, Gaussian emission distributions would typically be employed

$$b_j(o_t) = \mathcal{N}(o_t; \mu_j, \Sigma_j) \quad (68)$$

where μ_j and Σ_j represent the mean vector and covariance matrix for state j (Ghahramani & Jordan, 1997).

Forward Algorithm and State Inference. A forward algorithm would compute the probability of observing a sequence of Framework B patterns given the model parameters. The forward variable $\alpha_t(i)$ represents the probability of observing the sequence $o_1, o_2, \dots, o_t$ and being in state i at time t

$$\alpha_t(i) = P(o_1, o_2, \dots, o_t, q_t = i | \lambda) \quad (69)$$

The recursive computation would proceed as (70)

$$\alpha_1(i) = \pi_i b_i(o_1) \quad \alpha_{t+1}(j) = \left[\sum_{i=1}^N \alpha_t(i) a_{ij} \right] b_j(o_{t+1})$$

where N represents the number of hidden states (4 for BPD modeling; Baum et al., 1970).

Viterbi Algorithm for Optimal State Sequence. The Viterbi algorithm (a dynamic path-finding programming algorithm that extracts the optimal path through a trellis diagram representing possible state transitions to uncover the most likely sequence of hidden states in a

HMM that results in a time scale of observed events) would identify the most likely sequence of hidden states given observed Framework B patterns, enabling retrospective analysis of BPD emotional episodes. The algorithm would employ dynamic programming (see Chapter 2) to find the optimal state sequence

$$\delta_t(i) = \max P(q_1, q_2, \dots, q_{t-1}, q_t = i, o_1, o_2, \dots, o_t \mid \lambda) \quad (71)$$

The recursive computation is

$$\delta_i(i) = \pi_i b_i(o_1) \quad \delta_t(j) = [\max(\delta_{t-1}(i) a_{ij})] b_j(o_t) \quad (72)$$

with backtracking to recover the optimal state sequence (Viterbi, 1967; Forney, 1973).

Parameter Estimation and Learning. HMM parameters would be estimated using the Expectation-Maximization (EM) algorithm, specifically the Baum-Welch algorithm for HMMs. The E-step would compute expected sufficient statistics, while the M-step would update parameters to maximize the likelihood (Baum et al., 1970; Dempster et al., 1977).

The re-estimation formulas for continuous observation HMMs are

$$\hat{\pi}_i = \gamma_1(i) \quad (73)$$

$$(74)$$

$$\hat{a}_{ij} = \frac{\sum_{t=1}^{T-1} \xi_t(i, j)}{\sum_{t=1}^T \gamma_t(i)} \quad (75)$$

$$\hat{\mu}_j = \frac{\sum_{t=1}^T \gamma_t(j) o_t}{\sum_{t=1}^T \gamma_t(j)} \quad (76)$$

$$\hat{\Sigma}_j = \frac{\sum_{t=1}^T \gamma_t(j) (o_t - \hat{\mu}_j)(o_t - \hat{\mu}_j)^T}{\sum_{t=1}^T \gamma_t(j)}$$

where $\gamma_t(i)$ and $\xi_t(i,j)$ represent Bayesian posterior probabilities computed from forward-backward variables (Rabiner, 1989).

Architecture Specifications for HMM for BPD. The BPD HMM would employ four hidden states representing the emotional regulation cycle observed in clinical practice:

1. Stable: Baseline emotional regulation with normal Framework B patterns
2. Triggered: Initial stress response with emerging impulsivity indicators
3. Dysregulated: Active emotional dysregulation with elevated impulsivity across all Framework B components
4. Recovery: Gradual return to baseline with residual attention deficits

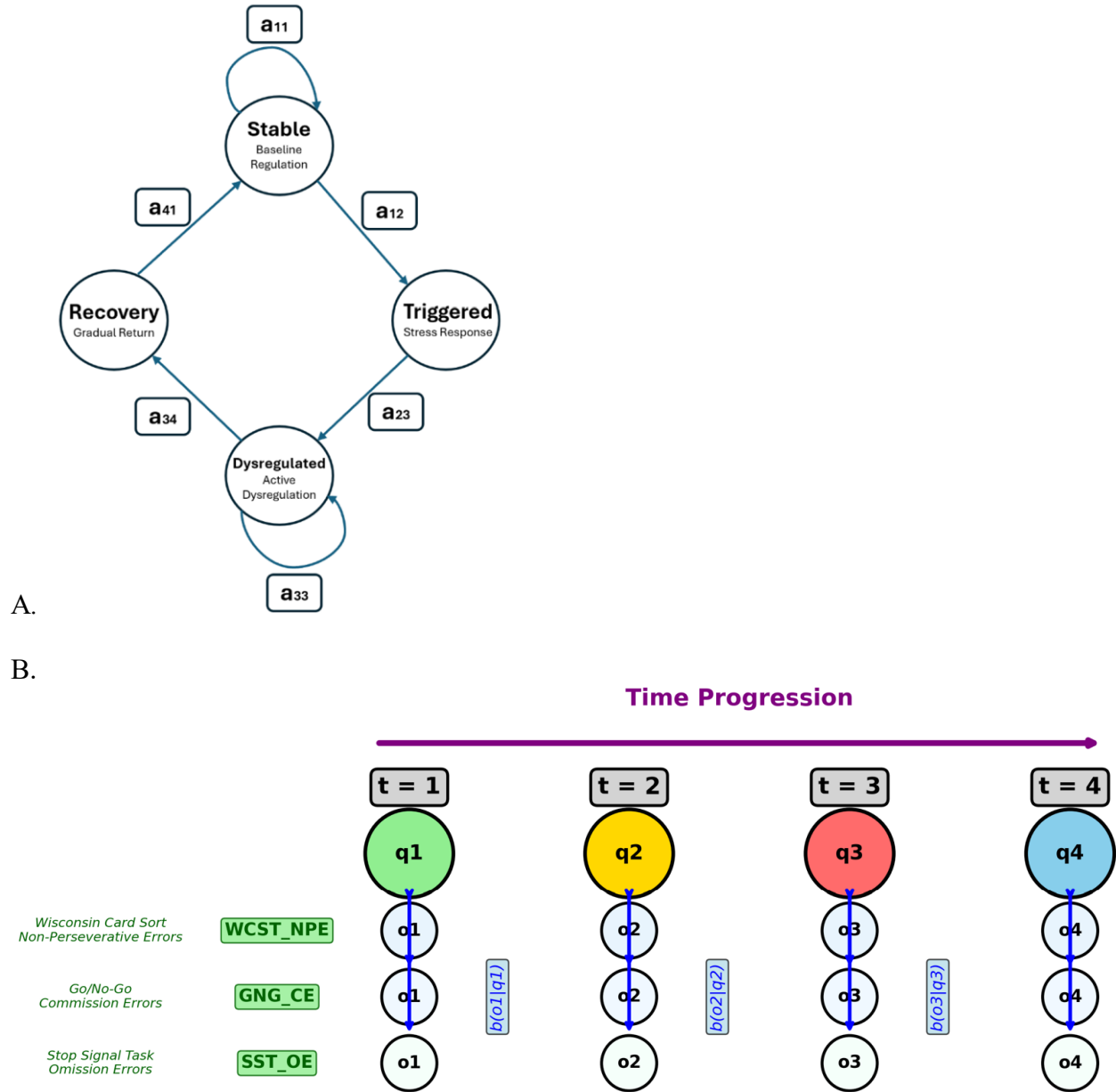
State transition probabilities would incorporate stress indicators as time-varying parameters, enabling the model to adapt transition likelihoods based on environmental (perturbational) factors. This could be implemented through switching HMMs where transition matrices depend on stress level s_t

$$\mathbf{A}(S_t) = (1 - s_t)\mathbf{A}_{baseline} + s_t\mathbf{A}_{stress} \quad (77)$$

where $\mathbf{A}_{baseline}$ and $\mathbf{A}_{stress}$ represent transition matrices for low and high stress conditions, respectively (Hamilton, 1989; Kim & Nelson, 1999). Figure 73 shows the HMM architecture using the above specifications.

Figure 73

Hidden Markov Model for BPD State Transition Modeling for Framework B



Note: Top A. shows temporal state transitional dynamics. Bottom B. shows temporal observation sequence. State transitions: $a_{ij} = P(q_{t+1} = j \mid q_t = i)$. Stress-Dependent Transitions: $A(s_t) = A_{\text{baseline}} + s_t A_{\text{stress}}$. Emissions: $b_j(o_t) = P(o_t \mid q_t = j)$. HMM Components: $\lambda = (A, B, \pi)$.

Clinical Applications of HMM for BPD. The HMM framework could enable several critical clinical applications for BPD intervention, treatment, and management. Crisis prediction might emerge from real-time state inference, where transitions into the *triggered* state could alert clinicians and patients to implement early intervention strategies before full dysregulation occurs (Glenn & Klonsky, 2009; Muehlenkamp et al., 2011).

Intervention timing optimization could use state probability distributions to determine optimal moments for different therapeutic interventions. Dialectical Behavior Therapy (DBT) skills coaching discussed in Chapter 2 might be most effective as a treatment modality during *triggered* states, while intensive stabilization approaches may be indicated during *dysregulated* states (Linehan, 2014; Stoffers et al., 2012).

The temporal modeling capability would enable longitudinal treatment monitoring, where changes in state transition probabilities and emission distributions could reflect treatment progress. Successful therapy should result in reduced transition probabilities to *dysregulated* states and faster recovery transitions, providing objective measures of therapeutic effectiveness (Links et al., 2015; Zanarini et al., 2003).

Alternative AI/ML/DL Approaches for Specialized Applications

While the primary neurocomputational model architectures described above provide suggested optimized solutions for specific behavioral phenotypes, several alternative AI/ML/DL approaches could offer complementary capabilities that enhance overall system performance and address specialized requirements. These alternative methods could serve as secondary components in ensemble frameworks, provide specialized preprocessing capabilities, or address specific challenges such as data scarcity (sparse data is a common issue with high dimensional data sets), temporal dynamics, and interpretability (explainable AI) requirements. The integration

of these approaches with the above primary architectures would create more robust and comprehensive neurocomputational models capable of handling the complex, multifaceted nature of behavioral phenotype presentations observed in clinical practice.

Graph Neural Networks for Comorbidity Modeling. The high comorbidity rates observed in this study (55.4% ADHD-ASD, 43% BPD-schizophrenia overlap) suggest that behavioral phenotypes exist within complex relational networks that traditional classification approaches struggle to capture effectively. Graph Neural Networks (GNNs; semi-supervised deep learning methods that can operate as black-box models) could provide mathematical frameworks for explicitly modeling these comorbidity relationships while incorporating Framework B features as node attributes within behavioral phenotype networks (Wu et al., 2020; Zhou et al., 2020).

Mathematical Foundation of GNNs. GNNs would operate on graph-structured data where behavioral phenotypes represent vertices $\mathbf{V}$ and comorbidity relationships represent edges $\mathbf{E}$. The adjacency matrix $\mathbf{A}$ established earlier could be enhanced with Framework B features as node attributes $\mathbf{X} \in \mathbb{R}^{n \times d}$ where n represents the number of participants and d represents the dimensionality of Framework B features.

Graph convolution operations would aggregate neighborhood information through spectral or spatial convolutions. A simplified Graph Convolutional Network (GCN) layer can be expressed as

$$\mathbf{H}^{l+1} = \sigma(\tilde{\mathbf{D}}^{-\frac{1}{2}} \tilde{\mathbf{A}} \tilde{\mathbf{D}}^{-\frac{1}{2}} \mathbf{H}^l \mathbf{W}^l) \quad (78)$$

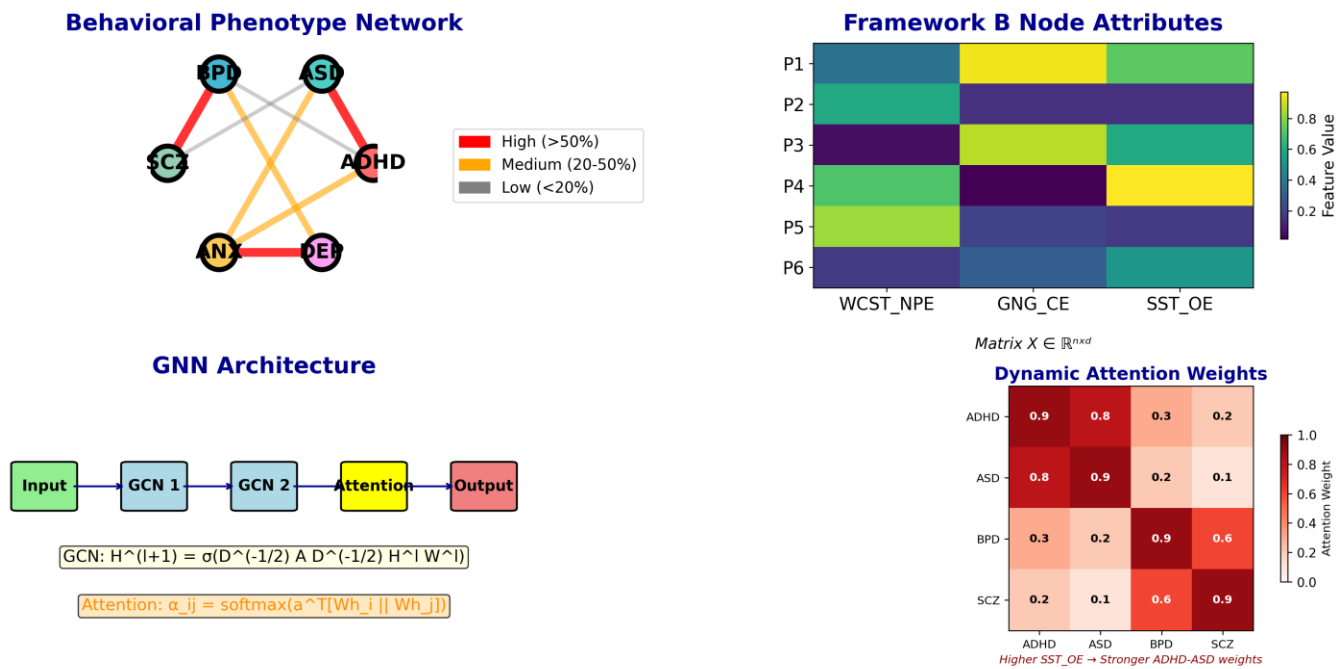
where $\mathbf{H}^l$ represents the node features at layer l , $\tilde{\mathbf{A}} = \mathbf{A} + \mathbf{I}$ represents the adjacency matrix with added self-connections, $\tilde{\mathbf{D}}$ represents the degree matrix, $\mathbf{W}^l$ represents learnable weight parameters, and σ represents the activation function (Kipf & Welling, 2016).

Architecture Specifications of GNN. The GNN architecture for comorbidity modeling would incorporate multiple layers of graph convolutions followed by pooling operations for behavioral phenotype-level predictions. Attention mechanisms could be integrated to enable dynamic weighting of comorbidity relationships based on individual presentations

$$\alpha_{ij} = softmax(LeakyReLU(\mathbf{a}^T[\mathbf{W}h_i || \mathbf{W}h_j])) \tag{79}$$

where α_{ij} represents the attention weight between behavioral phenotypes i and j , $\mathbf{a}$ represents learnable attention parameters, $\mathbf{W}$ represents transformation weights, and $||$ denotes concatenation (Veličković et al., 2017). Figure 74 illustrates the GNN, its node attributes, architecture, and dynamic attention weights.

Figure 74
Graph Neural Network for Comorbidity Modeling



Clinical Applications of GNNs. GNN approaches could enable dynamic comorbidity weighting where attention weights adjust based on individual Framework B presentations. For example, participants with high SST_OE scores might receive increased attention weights for ADHD-ASD comorbidity modeling, reflecting the attentional bridge between these behavioral phenotypes. This capability would support more nuanced differential diagnostic decision-making that explicitly accounts for behavioral phenotype interaction patterns (Rhee et al., 2019; Zitnik et al., 2018).

Variational Autoencoders for Probabilistic Phenotype Representations. While overparametrized autoencoders provide rich latent representations for ASD phenotype discovery, Variational Autoencoders (VAEs; unsupervised deep learning methods employing Bayesian inference with inherent interpretability through probabilistic outputs) could offer probabilistic alternatives that enable uncertainty quantification and generative modeling capabilities. VAEs would be particularly valuable for risk assessment applications where confidence intervals around phenotype behavioral predictions are essential for clinical decision-making (Kingma & Welling, 2013; Rezende et al., 2014).

Mathematical Foundation of VAEs. VAEs implement probabilistic encoders that map Framework B features to probability distributions rather than deterministic latent representations. The encoder would produce parameters for latent distributions

$$\mu = f_{\mu}(x), \sigma = f_{\sigma}(x) \quad (80)$$

$$Z \sim \mathcal{N}(\mu, \sigma^2 I) \quad (81)$$

where μ and σ represent the mean and standard deviation of the latent distribution, and Z represents the sampled latent variable (Doersch, 2016).

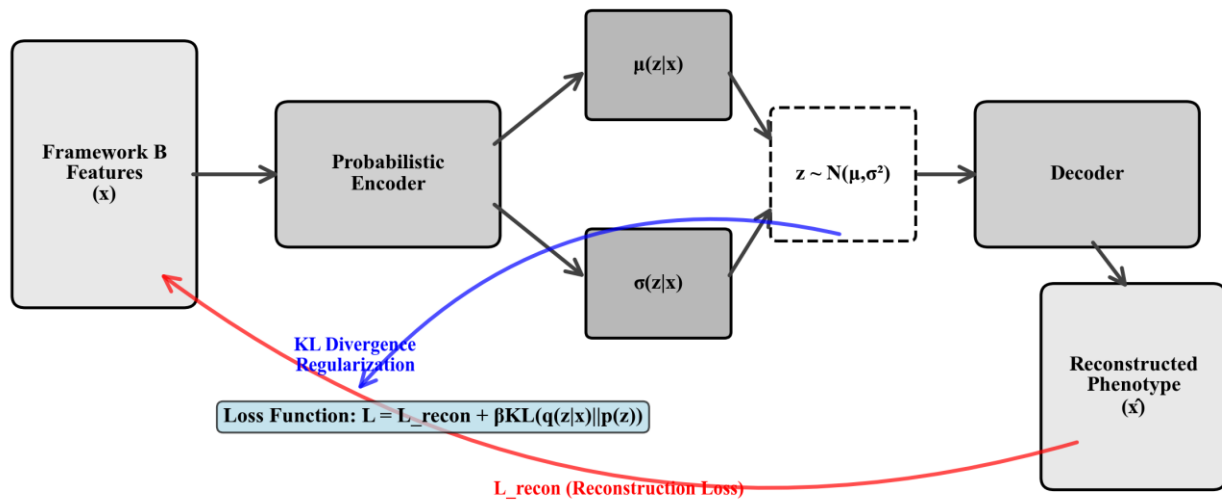
The VAE objective function combines reconstruction loss with KL divergence regularization

$$L = L_{recon} + \beta KL(q(z|x)||p(z)) \quad (82)$$

where L_{recon} represents the reconstruction loss, KL represents the Kullback-Leibler divergence between the approximate Bayesian posterior $q(z|x)$ and the Bayesian prior $p(z)$, and β controls the regularization strength (Higgins et al., 2016). Figure 75 illustrates the architecture of the above specified VAE.

Figure 75

Variational Autoencoder for ASD Phenotype Analysis



Note: Probabilistic encoder maps Framework B features to latent distributions enabling uncertainty quantification for clinical decision making.

Clinical Applications of VAEs. The probabilistic nature of VAE outputs could enable risk assessment with confidence intervals, where high-variance latent representations indicate uncertain behavioral phenotype assignments requiring additional clinical evaluation. Generative capabilities would allow synthesis of hypothetical behavioral phenotype profiles for treatment planning scenarios, enabling clinicians to explore “what-if” situations for intervention optimization (Blei et al., 2017; Ghahramani, 2015).

Transformer-Based Architectures for Sequential Pattern Analysis. For another alternative, BPD's temporal dynamics and the potential for longitudinal Framework B assessments suggest that sequential pattern analysis could provide valuable insights into behavioral phenotype trajectories. Encoder only transformer architectures (supervised deep learning methods with attention-based XAI capabilities) originally developed for natural language processing (NLP/LLM), could be adapted for time-series analysis of Framework B measurements to capture temporal dependencies and predict future states (Li et al., 2019; Vaswani et al., 2017).

Mathematical Foundation of Transformers. The core mechanism of transformers involves self-attention computations that enable modeling of long-range dependencies in sequential data. For Framework B time series $X = [x_1, x_2, \dots, x_t]$, the self-attention mechanism can be expressed as

(83)

$$Attention(\mathbf{Q}, \mathbf{K}, \mathbf{V}) = \text{softmax}\left(\frac{\mathbf{Q}\mathbf{K}^T}{\sqrt{dk}}\right)\mathbf{V}$$

where $\mathbf{Q}$, $\mathbf{K}$, and $\mathbf{V}$ represent query, key, and value matrices derived from linear transformations of the input sequence, and dk represents the dimensionality of the key vectors (Vaswani et al., 2017).

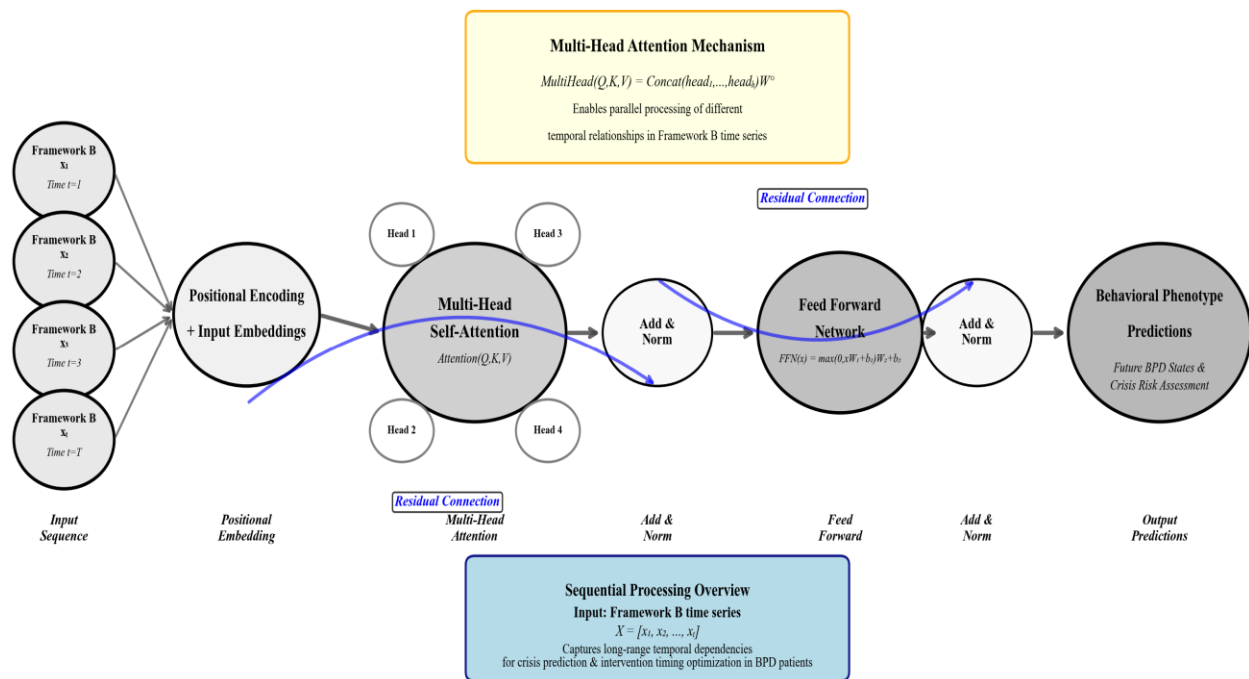
Multi-head attention would enable parallel processing of different types of temporal relationships

$$\text{MultiHead}(\mathbf{Q}, \mathbf{K}, \mathbf{V}) = \text{Concat}(\text{head}_1, \dots, \text{head}_h)W^O \quad (84)$$

where each head represents an independent attention computation, and W^O represents output projection weights (Devlin et al., 2018). Figure 76 illustrates the transformer architecture.

Figure 76

Transformer Architecture for Sequential Framework B Analysis



Note: Encoder-only transformer for temporal behavioral phenotype prediction in borderline personality disorder crisis monitoring.

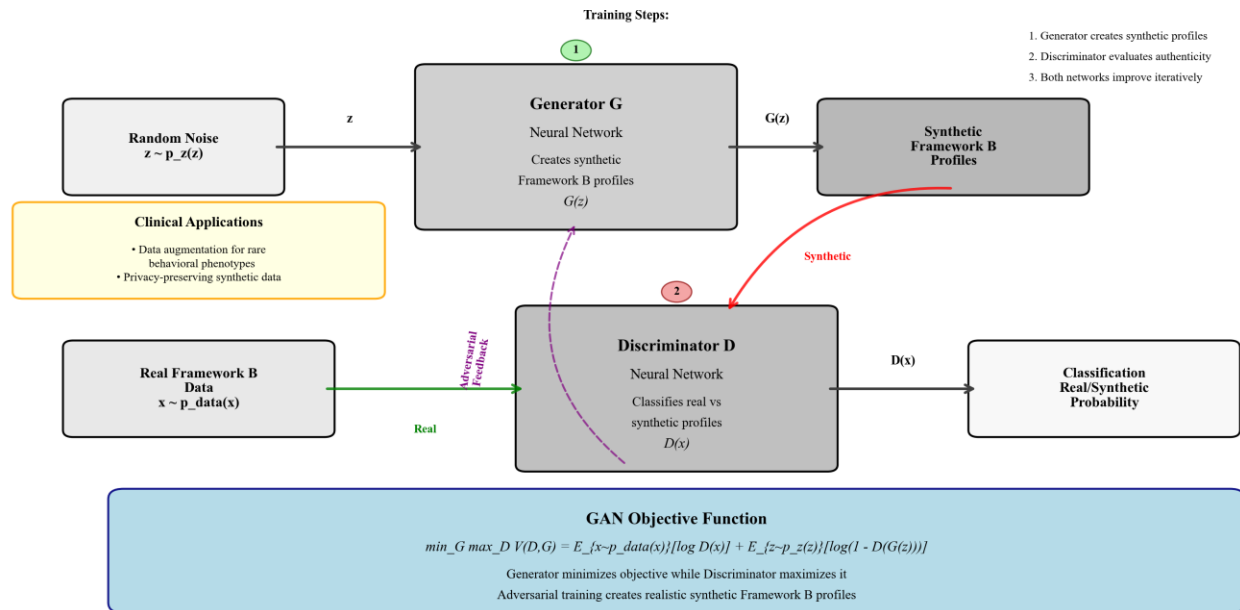
Clinical Applications of Transformers. Transformer-based approaches could enable dynamic behavioral phenotype prediction over time, where longitudinal Framework B assessments would be analyzed to predict future behavioral states and optimal intervention timing. For example, this capability could be particularly valuable for BPD crisis prediction and treatment monitoring, where temporal patterns in Framework B components could provide early warning signals for emotional dysregulation episodes (Che et al., 2018; Rajkomar et al., 2018).

Generative Adversarial Networks for Data Augmentation. The challenge of limited data availability for rare behavioral phenotype combinations (e.g., complex comorbidity patterns) could be addressed through Generative Adversarial Networks (GANs; unsupervised deep learning methods that function as black-box generative models) that generate synthetic Framework B profiles for training data augmentation. GANs would be particularly valuable for balanced dataset creation and handling of underrepresented behavioral phenotype combinations (Arjovsky et al., 2017; Goodfellow et al., 2014).

Mathematical Foundation of GANs. GANs involve adversarial training between a generator G that creates synthetic Framework B profiles and a discriminator D that attempts to distinguish real from synthetic profiles. The objective function can be expressed as (85)

$$\min \max V(D, G) = \mathbb{E}_{x \sim p_{data}(x)} [\log D(x)] + \mathbb{E}_{z \sim p_z(z)} [\log (1 - D(G(z)))]$$

where $p_{data}(x)$ represents the real data distribution, $p_z(z)$ represents the noise distribution, and the generator attempts to minimize while the discriminator attempts to maximize the objective function (Goodfellow et al., 2014). Figure 77 illustrates the above GAN architecture.

Figure 77*Generative Adversarial Network Architecture for Framework B Data Augmentation*

Clinical Applications and Regulatory Considerations of GANs. Synthetic data generation would enable training of robust models for rare behavioral phenotype combinations while maintaining privacy protection through data anonymization. However, regulatory considerations for synthetic medical data would require careful validation to ensure that generated profiles maintain clinical validity and do not introduce systematic biases that could affect differential diagnostic accuracy (Chen et al., 2021; Jordon et al., 2018).

Additional Specialized Methods. Several additional neurocomputational AI/ML/DL approaches can provide specialized capabilities for specific aspects of behavioral phenotype modeling. These alternative approaches would complement the primary model architectures described above, or incorporated into ensemble methods, by providing specialized capabilities for handling specific challenges in behavioral phenotype modeling, from temporal dynamics and data scarcity (sparse data) to interpretability and uncertainty quantification requirements.

Bayesian Neural Networks. BNNs (supervised deep learning methods employing Bayesian inference with inherent uncertainty quantification) would enable uncertainty-aware predictions by treating network weights as probability distributions rather than point estimates. This approach could provide confidence intervals around behavioral phenotype predictions, enabling clinical decision thresholds based on prediction uncertainty (Gal & Ghahramani, 2016; Kendall & Gal, 2017).

Meta-Learning Approaches. Meta-learning, supervised machine learning methods that employ learning-to-learn adaptive learning algorithms, could address so called few-shot learning challenges for rare behavioral phenotype presentations by learning to rapidly adapt to new behavioral phenotype combinations with limited training data. This capability would be particularly valuable for handling novel comorbidity patterns not represented in training datasets (Finn et al., 2017; Hospedales et al., 2021).

Reinforcement Learning. RL (model-free machine learning methods that employ reward-based optimization that can provide interpretable policy decisions) could enable adaptive treatment recommendation systems where therapeutic interventions are optimized based on observed Framework B responses over time. The framework would treat behavioral states as environmental states and interventions as actions, with treatment outcomes serving as rewards for policy optimization (Komorowski et al., 2018; Yu et al., 2019).

Self-Organizing Maps. SOMs (unsupervised machine learning methods with inherent XAI visualization capabilities) would provide clinician-interpretable visualization of behavioral phenotype relationships through dimensionality reduction that preserves topological structure. This approach could support clinical training and decision support by providing intuitive 2D

representations of complex behavioral phenotype spaces (Kohonen, 2013; Vesanto & Alhoniemi, 2000).

Hierarchical Bayesian Models. HBMs (supervised machine learning methods employing hierarchical Bayesian inference with interpretable probabilistic outputs) could capture multi-level structure in behavioral phenotypes, modeling individual endophenotypes, syndrome clusters, and behavioral phenotype categories within unified probabilistic frameworks. This approach would enable analysis of behavioral phenotype structure at multiple levels of abstraction while maintaining uncertainty quantification (Gelman et al., 2013; Kruschke, 2014).

While the individual model architectures described above provide specialized capabilities tailored to specific behavioral phenotype characteristics, the complex, multifaceted nature of behavioral presentations observed in this study necessitates integrated approaches that transcend single-model limitations. The high comorbidity rates identified—particularly the 55.4% ADHD-ASD overlap and 43% BPD-schizophrenia overlap—demonstrate that behavioral phenotypes exist within interconnected networks that require sophisticated mathematical integration frameworks. Furthermore, the varying reliability of different modeling approaches across different presentation patterns suggests that static, single-model solutions cannot adequately address the full spectrum of clinical scenarios encountered in research and clinical practice. Ensemble digital twin architectures address these limitations by combining the specialized strengths of multiple AI paradigms through principled mathematical integration that maintains both predictive accuracy and clinical interpretability.

Ensemble Digital Twin Architecture

The ensemble digital twin architecture embodies the NDST-informed theoretical framework described in Chapter 2 and empirically operationalized in Chapter 4, where reductionist endophenotype decomposition serves as the essential foundation for emergent systems modeling rather than its antithesis. The identification of multiple statistically significant framework combinations (A, B, C, D) demonstrates that complex behavioral control systems exhibit rich dimensional structure that dimensional reduction techniques may inadvertently obscure. Framework B's emergence as the most optimal combination of power and parsimony, partial $\eta^2 = .040$, while maintaining computational tractability, exemplifies the optimal balance between reductionist precision and emergent complexity. The ensemble approach leverages this principle by integrating specialized model architectures—each optimized for specific reductionist components (NPE for prefrontal dysfunction, GNG_CE for motor inhibition, SST_OE for attention regulation)—into emergent digital twins capable of capturing the complex, multifactorial presentations observed across behavioral phenotypes. This progression from "precise decomposition of system elements" to "sophisticated modeling of their complex interactions" validates the NDST informed proposition from Chapter 2 that emergent phenomena emerge from, rather than despite, careful reductionist analysis of their constituent components.

As described above, the individual model architectures described previously provide specialized capabilities for specific behavioral phenotypes, but the complex, multifactorial nature of behavioral presentations observed in this study—particularly the high comorbidity rates (55.4% ADHD-ASD, 43% BPD-schizophrenia overlap)—necessitates ensemble approaches that leverage the complementary strengths of multiple AI neurocomputational modeling paradigms. Digital twin architectures represent comprehensive mimetic computational models that can

simulate, predict, and optimize behavioral phenotype presentations through integrated ensemble frameworks (Rasheed et al., 2020; Vollmer et al., 2020). These ensemble systems would combine the strengths of different AI approaches while mitigating individual model limitations through sophisticated mathematical integration frameworks that enable uncertainty quantification, robust prediction, and clinical interpretability.

The ensemble digital twin concept extends beyond simple model averaging to create dynamic, adaptive systems that can weight component models based on individual presentations, incorporate temporal dynamics, and provide multi-level insights from behavioral endophenotype patterns to clinical recommendations. Framework B components would serve as validated input features across all ensemble components, ensuring consistent feature representation while enabling each specialized model to contribute its unique analytical capabilities to the comprehensive behavioral phenotype assessment.

Mathematical Integration Framework for Ensemble Methods. The foundation of ensemble digital twin architecture requires sophisticated mathematical frameworks for combining predictions from heterogeneous model types while maintaining theoretical rigor and clinical interpretability. The ensemble integration would extend beyond traditional weighted averaging to incorporate Bayesian model averaging, temporal consistency constraints, and uncertainty propagation through complex model combinations.

Ensemble Formulation. Ensemble integration for behavioral phenotype neurocomputational applications extends beyond traditional weighted averaging approaches to incorporate adaptive, context-dependent model combination strategies. The fundamental ensemble prediction for behavioral phenotype k can be expressed as a weighted combination of component model outputs

$$\hat{y}_k = \sum_{i=1}^M w_i f_i(x)$$

where w_i represents the weight for model i , $f_i(x)$ represents the prediction from model i given Framework B input x , M represents the total number of component models, and $\sum_i w_i = 1$ (Dietterich, 2000).

However, static weighting proves insufficient for behavioral phenotype applications due to varying model reliability across different presentation patterns, necessitating adaptive weighting mechanisms that adjust based on prediction confidence and model expertise for specific clinical scenarios (87)

$$w_i(x) = \frac{\exp(g_i(x))}{\sum_{j=1}^M \exp(g_j(x))}$$

where $w_i(x)$ the attention weight for position i , $g_i(x)$ represents a learned gating function (logit raw attention score) that determines model i 's expertise for input x , and M represents the total number of positions/elements (Jacobs et al., 1991; Jordan & Jacobs, 1994).

Bayesian Model Averaging. For applications requiring rigorous uncertainty quantification, Bayesian model averaging would provide principled integration of model predictions with associated confidence measures (88)

$$P(y|x, D) = \sum_{i=1}^M P(y|x, M_i, D)P(M_i|D)$$

where $P(y|x, M_i, D)$ represents the prediction from model M_i given data D , and $P(M_i|D)$ represents the Bayesian posterior probability of model M_i given the observed data (Hoeting et al., 1999; Fragoso et al., 2018).

The model posterior probabilities would be computed through Bayesian model comparison using information criteria or cross-validation performance

$$P(M_i|D) \propto P(D|M_i)P(M_i) \quad (89)$$

where $P(D|M_i)$ represents the marginal likelihood and $P(M_i)$ represents the model prior (Kass & Raftery, 1995).

Meta-Learning Optimization. The ensemble weights would be optimized through meta-learning algorithms that learn to combine model predictions based on their historical performance across different behavioral phenotype presentations

$$L_{meta} = \sum_{t=1}^T L(\hat{y}_t, y_t) + \lambda \Omega(w)$$

where $L(\hat{y}_t, y_t)$ represents the loss for prediction $\hat{y}_t$ versus true label y_t at time t , λ represents the regularization parameter, and $\Omega(w)$ represents a regularization term encouraging diverse ensemble weights (Finn et al., 2017; Hospedales et al., 2021).

Uncertainty Propagation. Uncertainty propagation through ensemble predictions requires careful mathematical treatment to avoid underestimating prediction variance. For models with Gaussian prediction distributions, the ensemble uncertainty can be decomposed into epistemic (model) and aleatoric (data) components

$$\Sigma^2_{ensemble} = \sigma^2_{epistemic} + \sigma^2_{aleatoric} \quad (91)$$

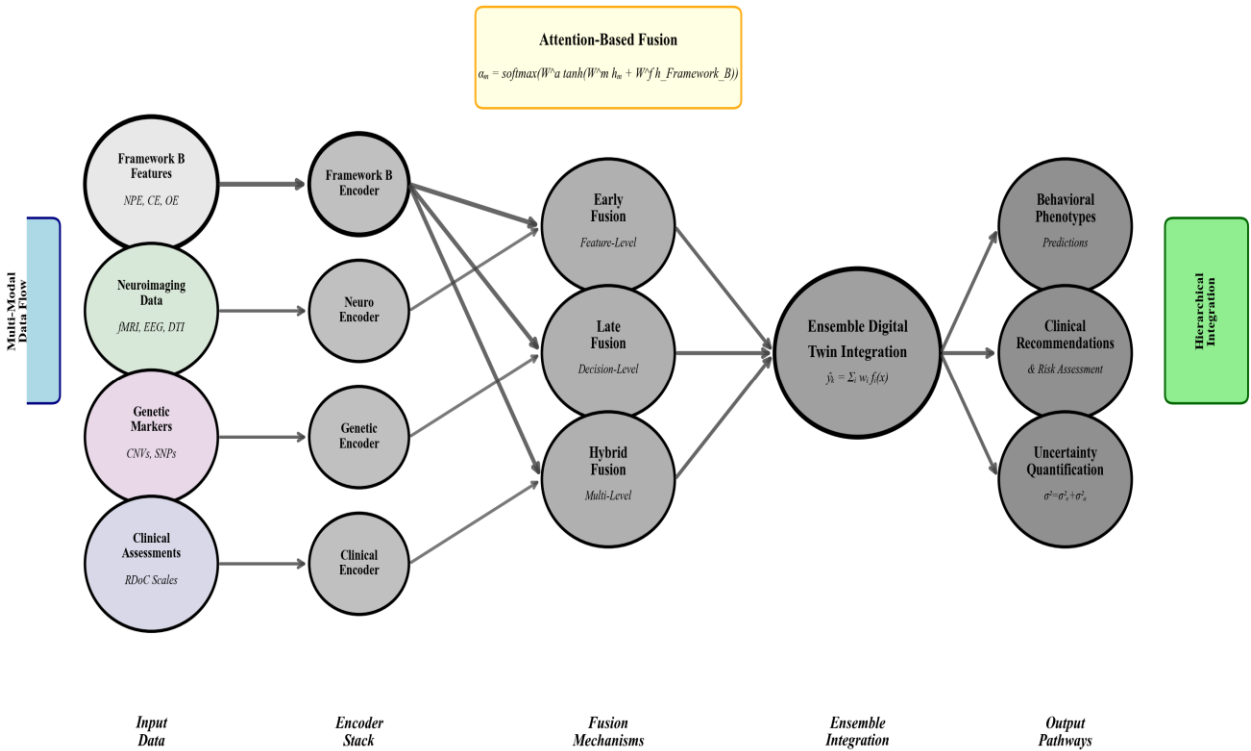
where the epistemic uncertainty reflects disagreement between models and aleatoric uncertainty reflects inherent data noise (Kendall & Gal, 2017). This decomposition would enable clinical decision-making based on uncertainty type, where high epistemic uncertainty indicates need for additional data collection and high aleatoric uncertainty indicates inherent behavioral phenotype ambiguity.

Multi-Modal Fusion Framework. The ensemble digital twin architecture would incorporate multi-modal data fusion capabilities that extend beyond Framework B (neuropsychological and neurobiological) features to integrate additional RDoC scales of measure including neuroimaging (neurophysiological), genetic (neurobiological), and clinical assessment data when available. This multi-modal integration would follow hierarchical fusion approaches that preserve the interpretability advantages of Framework B while enhancing prediction accuracy through complementary transdiagnostic and scale agnostic data sources. The multi-modal fusion architecture directly implements the comprehensive Generic Model Study framework described in Chapter 2, exemplifying the postulate described in Chapter 2 that reductionist decomposition arguably enables rather than opposes NDST enabled emergent systems modeling. The validated Framework B deep endophenotypes serve as precisely decomposed system elements that, when integrated with genetic polymorphisms (e.g., DRD4-7R VNTR, COMT Val158Met), neuroimaging data (fMRI circuit mapping, EEG/ERP eLORETA spatiotemporal analysis), and clinical assessment modalities (MMPI-2-RF, MCMI-IV), create emergent digital twin capabilities that transcend the sum of their individual components.

This reductionist→emergent progression demonstrates that careful dimensional decomposition of complex behavioral control systems provides the essential foundation for sophisticated emergent modeling approaches, where precisely characterized elements enable understanding of their complex interactions rather than obscuring them through premature dimensional reduction. The empirical validation of multiple significant framework combinations (A, B, C, D) supports the theoretical proposition that different dimensional decompositions may reveal distinct aspects of complex system dynamics, with Framework B's three feature deep endophenotypes optimal power-parsimony balance, partial $\eta^2 = .040$, and Framework A's

(Optimal Performance) five feature endophenotypes largest effect size combination, partial $\eta^2 = .046$, indicating optimal discrimination for motor impulsivity while alternative frameworks capture complementary behavioral control mechanisms. The comprehensive multi-modal fusion architecture is illustrated in Figure 78 showing the integration of input layers, encoder stacks, fusion mechanisms, and output pathways.

Figure 78
Fusion Ensemble Digital Twin Architecture



Attention-Based Fusion. Multi-modal attention mechanisms would enable adaptive weighting of different data modalities based on their relevance for specific behavioral phenotype presentations

$$\alpha_m = \text{softmax}(\mathbf{W}_a \tanh(\mathbf{W}_m \mathbf{h}_m + \mathbf{W}_f \mathbf{h}_{\text{Framework\_B}})) \quad (92)$$

where α_m represents the attention weight for modality m , $\mathbf{h}_m$ represents the encoded representation from modality m , $\mathbf{h}_{\text{Framework\_B}}$ represents the Framework B encoding, and $\mathbf{W}_a$, $\mathbf{W}_m$, $\mathbf{W}_f$ represent learnable attention parameters (Bahdanau et al., 2014; Vaswani et al., 2017).

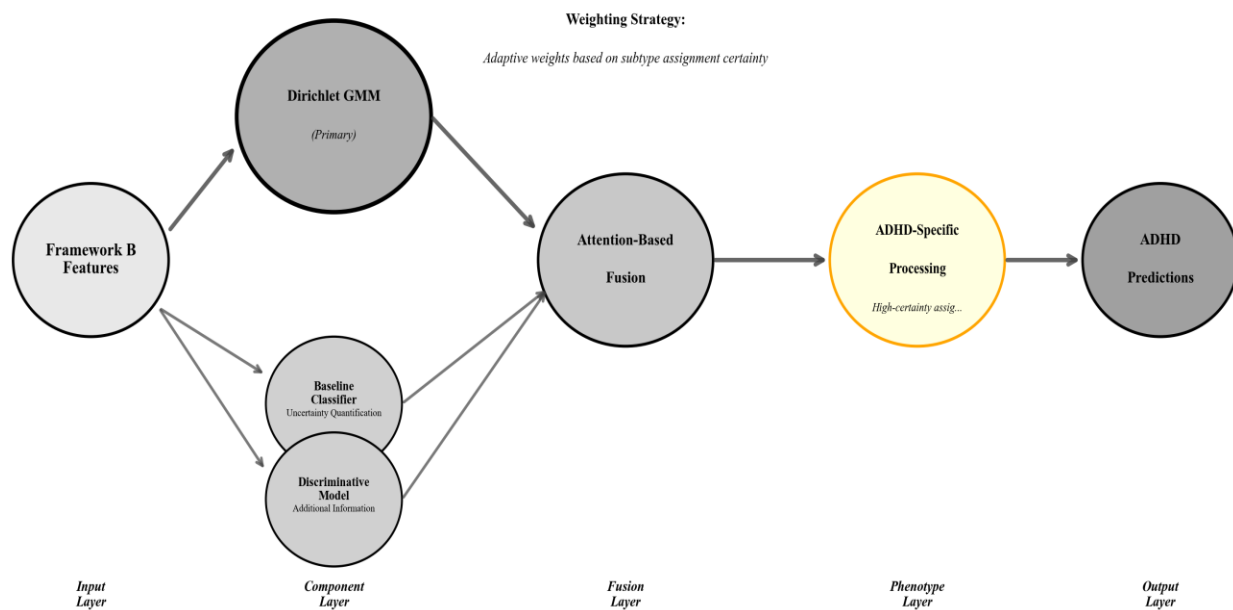
Behavioral Phenotype-Specific Digital Twin Implementation. Each behavioral phenotype would receive a specialized digital twin configuration that optimizes ensemble weights and component selection based on behavioral phenotype-specific characteristics and clinical requirements. These implementations would leverage the findings from this study regarding optimal deep endophenotype combinations as well as comorbidity patterns.

ADHD Digital Twin. The ADHD digital twin configuration (Figure 79) would prioritize the Dirichlet GMM as the primary component due to ADHD's heterogeneous subtype structure, with secondary components providing baseline comparisons and uncertainty quantification. The ensemble weighting for ADHD would adapt based on the certainty of subtype assignment from the Dirichlet GMM. High-certainty assignments would increase the Dirichlet GMM weight, while uncertain assignments would increase the weight of secondary components to provide additional discriminative information.

The ADHD digital twin configuration leverages the empirical finding from Chapter 4 that individuals with high trait motor impulsivity achieve optimal performance at 558ms reaction time thresholds compared to 625ms for low trait motor impulsivity individuals. This 67-millisecond optimization difference challenges conventional *slow down* intervention approaches and suggests that ADHD digital twins should incorporate faster-paced processing algorithms that work with, rather than against, optimal neural efficiency patterns. The Dirichlet GMM component weights would adapt based on individual reaction time threshold profiles, enabling personalized model configurations that capitalize on faster processing capabilities.

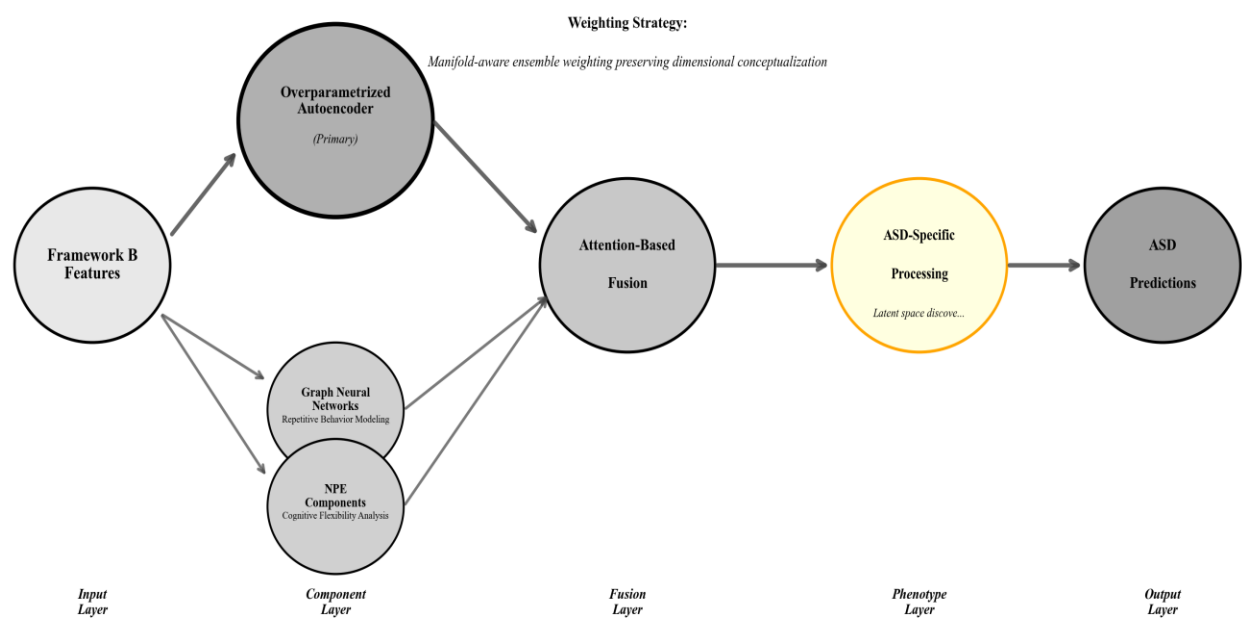
Figure 79

ADHD Digital Twin Architecture



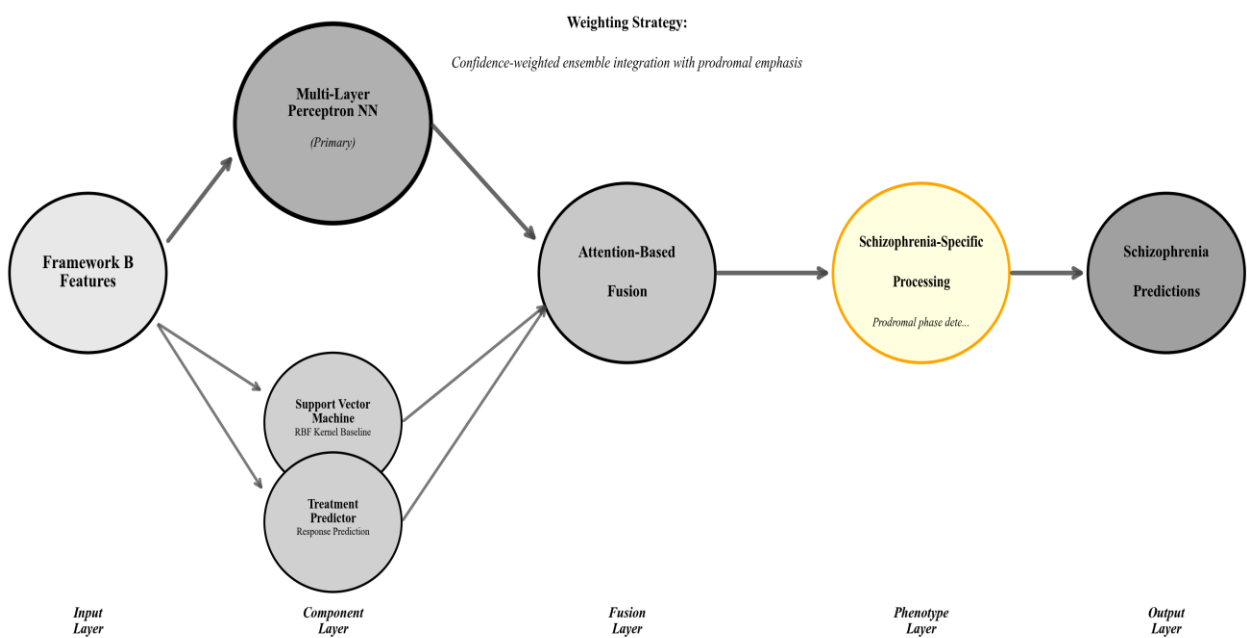
ASD Digital Twin. The ASD digital twin configuration (Figure 80) would emphasize the overparametrized autoencoder for latent dimensional discovery while incorporating graph neural networks (GNNs) to model repetitive behavior patterns. This architecture would employ manifold-aware ensemble weighting that preserves the dimensional conceptualization of autism spectrum presentations while emphasizing NPE contributions reflecting cognitive flexibility deficits.

Figure 80
ASD Digital Twin Architecture



Schizophrenia Digital Twin. The schizophrenia digital twin configuration (Figure 81) would prioritize the MLPNN for robust classification while incorporating support vector machines (SVMs) with RBF kernels for non-linear baseline comparisons. This architecture would employ confidence-weighted ensemble integration with emphasis on prodromal phase sensitivity and treatment response prediction capabilities.

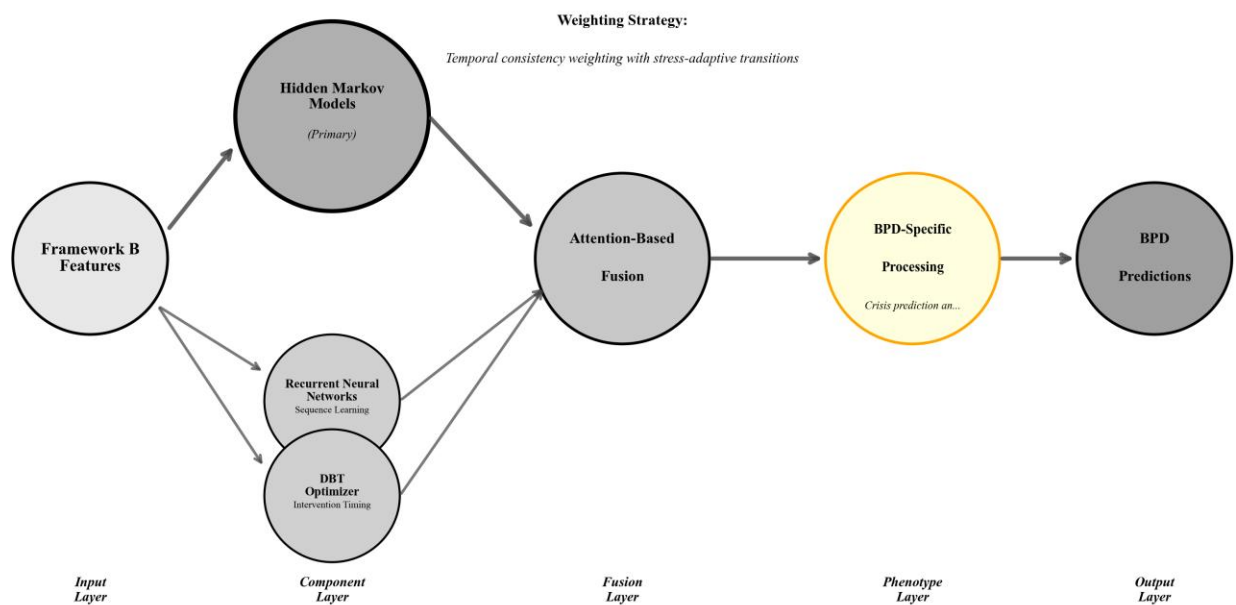
Figure 81
Schizophrenia Digital Twin Architecture



BPD Digital Twin. The BPD digital twin configuration (Figure 82) would emphasize temporal modeling through HMMs while incorporating recurrent neural networks (RNNs) for sequence learning comparison. This architecture would employ temporal consistency weighting with stress-adaptive transitions optimized for DBT intervention timing and crisis prediction applications.

Figure 82

BPD Digital Twin Architecture



Federated Learning Framework for Multi-Site Implementation. The ensemble digital twin architecture would incorporate federated learning capabilities to enable training across multiple clinical sites without centralizing sensitive patient data. This approach would be particularly valuable for accumulating sufficient data for rare behavioral phenotype combinations while maintaining HIPAA compliance and data governance requirements.

Mathematical Foundation of Federated Learning. Federated learning for ensemble digital twins would employ distributed optimization where each site maintains local model replicas while contributing to global ensemble weight optimization (93)

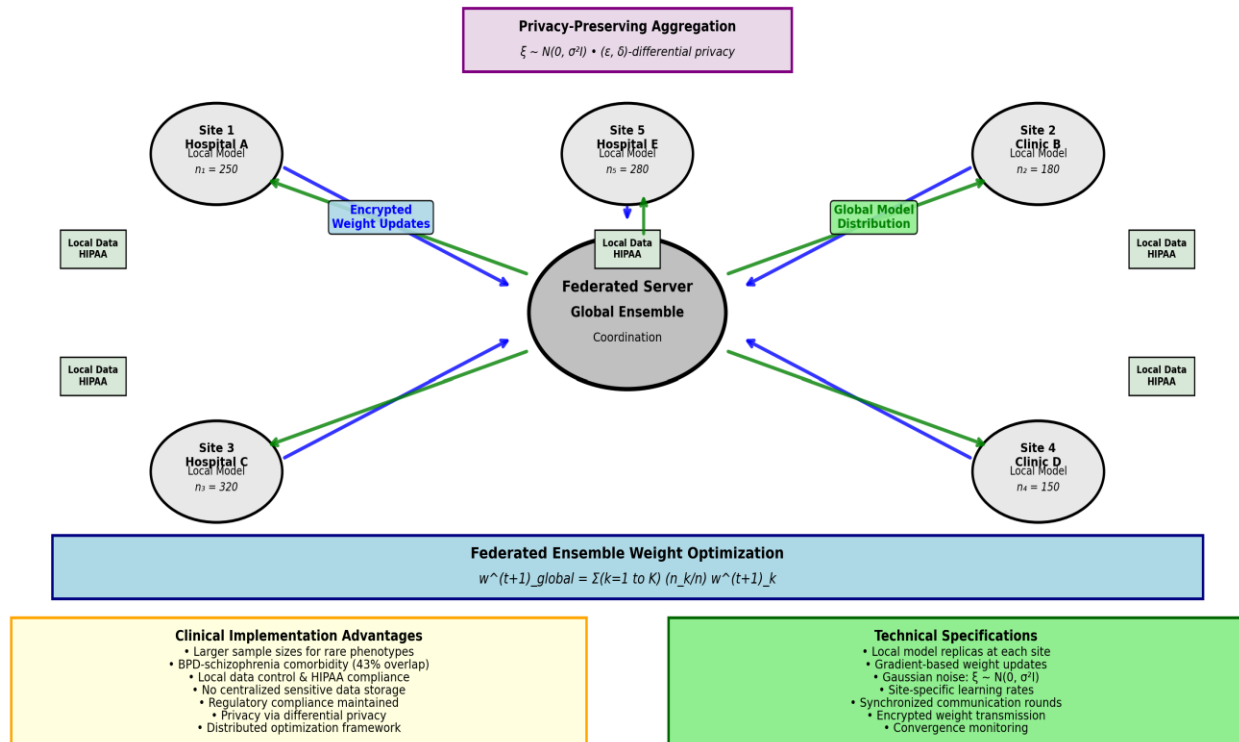
$$w^{t+1}global - \sum_{k=1}^K \left(\frac{n_k}{n}\right) w^{t+1}k$$

where $w^{t+1}global$ represents the global ensemble weights, $w^{t+1}k$ represents the local weights from site k , n_k represents the number of participants at site k , n represents the total participants across all sites, and K represents the number of participating sites (Li et al., 2020; McMahan et al., 2017).

Privacy-Preserving Aggregation. Differential privacy mechanisms would be incorporated to protect individual participant information during federated aggregation

$$w^{t+1}k = w^tk - \eta \nabla Lk(w^tk) + \xi \quad (94)$$

where η represents the learning rate, ∇Lk represents the local gradient, and $\xi \sim \mathcal{N}(0, \sigma^2 I)$ represents Gaussian noise calibrated to provide (ϵ, δ) -differential privacy (Abadi et al., 2016; Dwork & Roth, 2014). Figure 83 illustrates a federated framework implemented from this study.

Figure 83*Federated Learning Framework for Multisite Implementation*

Clinical Implementation Advantages of Federated Learning. Federated learning would enable larger effective sample sizes for rare behavioral phenotype combinations while maintaining local data control. For example, BPD-schizophrenia comorbidity (43% overlap observed) could be studied across multiple sites without centralizing sensitive psychiatric data, enabling more robust ensemble training while preserving privacy and regulatory compliance (Rieke et al., 2020; Xu et al., 2021).

The ensemble digital twin architecture represents a comprehensive framework for integrating multiple AI approaches into clinically deployable systems that can handle the complex, multifactorial nature of behavioral phenotype presentations while maintaining interpretability and regulatory compliance essential for clinical adoption. The sophisticated

neurocomputational architectures described above—from individual specialized models to complex ensemble digital twins—represent powerful analytical frameworks capable of advanced behavioral phenotype modeling and prediction. However, the transition from research prototypes to clinical deployment requires addressing fundamental challenges of interpretability, transparency, and regulatory compliance that extend far beyond predictive performance metrics.

Healthcare applications demand not only accurate predictions but also explanations that clinicians can understand, validate, and defend in clinical practice. Moreover, regulatory agencies require comprehensive evidence of safety, effectiveness, and transparent decision-making processes before approving AI systems for clinical use. The complex mathematical frameworks underlying ensemble digital twins (particularly deep learning multi-layer artificial neural networks), while computationally powerful, often operate as *black boxes* that obscure the reasoning pathways leading to specific clinical recommendations (i.e., they provide the outputs, but cannot explain how they arrived at those outputs so they lack causality or mechanistic explanation). This opacity creates untenable situations for clinical practice, where healthcare providers must make evidence-based decisions while bearing legal and ethical responsibility for patient outcomes.

Explainable AI (XAI) and Regulatory Framework

The deployment of neurocomputational AI systems from computational psychiatry in clinical settings, particularly for diagnostic and treatment decision support, necessitates comprehensive approaches to model interpretability and causal understanding that extend far beyond traditional performance metrics. The complex behavioral phenotype modeling architectures described above, while powerful in their predictive capabilities, must provide

transparent, interpretable, and causally grounded explanations to meet regulatory requirements and clinical practice standards essential for patient safety and professional liability protection.

Explainable and Causal AI Foundational Concepts. Understanding the foundational concepts of explainable and causal AI provides the essential conceptual framework for developing clinically appropriate behavioral phenotype models. These concepts establish the theoretical basis for interpretability requirements for federal agencies and demonstrate why traditional *black-box* (mostly deep learning) approaches are insufficient for regulated healthcare applications. The following subsections examine each foundational concept in detail, establishing the knowledge base necessary for implementing technical XAI solutions in clinical practice.

What is Explainable AI (XAI)? Explainable Artificial Intelligence (XAI) represents a paradigm of machine learning and artificial intelligence that enables human users to understand, appropriately trust, and effectively manage AI systems through transparent decision-making processes (Adadi & Berrada, 2018; Gunning et al., 2019). Unlike traditional *black-box* models that provide predictions without revealing their internal reasoning mechanisms, XAI systems offer interpretable explanations that illuminate the relationship between input features and model outputs, enabling clinicians to understand why specific diagnostic or treatment recommendations are generated by the model.

XAI encompasses multiple dimensions of interpretability that are particularly relevant for behavioral phenotype modeling. Global interpretability of a digital twin model for a behavioral phenotype from this study would reveal overall model behavior and feature importance patterns across entire datasets, enabling understanding of general relationships between Framework B components and behavioral phenotype classifications (Molnar, 2020). Local interpretability

would provide explanations for individual predictions, showing why a specific participant received a particular behavioral phenotype classification based on their unique Framework B profile (Ribeiro et al., 2016). Post-hoc interpretability would generate explanations after model training, while intrinsic interpretability would build explanation capabilities directly into model architectures during development (Rudin, 2019).

The mathematical foundation of XAI relies on attribution methods that decompose model predictions into contributions from individual input features. For a prediction function $f(x)$ where x represents Framework B features, an explanation method assigns attribution scores $\varphi = [\varphi_1, \varphi_2, \varphi_3]$ such that

(95)

$$f(x) \approx \varphi_0 + \sum_i \varphi_i$$

where φ_0 represents the baseline prediction and φ_i represents the contribution of Framework B component i to the final prediction (Lundberg & Lee, 2017).

What is Causal AI? Causal Artificial Intelligence represents a fundamental advancement beyond traditional correlational machine learning by explicitly modeling causal relationships between variables rather than merely identifying statistical associations (Pearl & Mackenzie, 2018; Peters et al., 2017). While conventional AI systems and models excel at pattern recognition and prediction based on statistical correlations and inferences, causal AI systems can answer counterfactual questions, understand intervention effects, and provide mechanistic explanations that align with human causal reasoning essential for clinical decision-making.

The distinction between correlation and causation becomes particularly critical in behavioral phenotype modeling, where spurious correlations between Framework B components and phenotype classifications could lead to ineffective, contraindicated, or harmful clinical

interventions. Causal AI employs mathematical frameworks from causal inference to distinguish genuine causal relationships from confounding associations (Hernán & Robins, 2020).

Causal AI systems operate through three levels of causal reasoning established by Pearl (2009): association (observational correlations), intervention (effects of actions), and counterfactuals (retrospective reasoning about alternative scenarios). For behavioral phenotype applications informed by the findings of this study, this hierarchy enables, for example, progression from identifying that high GNG_CE scores associate with ADHD diagnoses (association) to understanding that improving motor inhibition through targeted interventions reduces ADHD symptom severity (intervention) to reasoning about whether a participant would have developed different symptoms under alternative developmental conditions (counterfactuals).

Mathematical representations of causal relationships employ directed acyclic graphs (DAGs) where nodes represent variables and edges represent causal relationships. For Framework B components, a causal DAG might specify

$$\text{NPE} \rightarrow \text{Cognitive\_Flexibility} \rightarrow \text{Executive\_Function} \rightarrow \text{ADHD\_Symptoms}$$

$$\text{GNG\_CE} \rightarrow \text{Motor\_Inhibition} \rightarrow \text{Impulse\_Control} \rightarrow \text{ADHD\_Symptoms}$$

$$\text{SST\_OE} \rightarrow \text{Attention\_Regulation} \rightarrow \text{Sustained\_Attention} \rightarrow \text{ADHD\_Symptoms}$$

where arrows indicate causal direction and intermediate variables represent mechanistic pathways (Pearl, 2009; Spirtes et al., 2000).

Why XAI and Causal AI are Required for Regulated Industries. The imperative for explainable and causal AI in life sciences, computational psychiatry, diagnostic, and clinical applications stems from convergent regulatory, ethical, legal, and clinical practice requirements. These requirements prioritize patient safety, professional accountability, and evidence-based

medicine principles over pure predictive performance (Holzinger et al., 2017; Tjoa & Guan, 2020). They can be described by at least four key considerations.

First, regulatory requirements that optimize patient safety are paramount. The U.S. Food and Drug Administration (FDA) has established comprehensive guidelines for Software as Medical Device (SaMD) that explicitly require transparency and interpretability for AI systems used in clinical decision support (FDA, 2021, 2024). The FDA's Action Plan for AI/ML-Based Medical Devices emphasizes that “patients and providers must be able to understand the basis for AI/ML device outputs” and mandates that manufacturers provide “clear information about when and how the algorithm was trained, how it should be used, and what its limitations are” (FDA, 2021, p. 8).

These regulatory requirements reflect fundamental patient safety concerns where unexplained AI recommendations could lead to inappropriate diagnoses, failed differential diagnosis, ineffective or contraindicated treatments, or delayed interventions with potentially serious consequences. In behavioral phenotype applications, incorrect classifications could result in inappropriate medication prescriptions (e.g., stimulants for non-ADHD presentations or where bipolar I disorder is comorbid), ineffective behavioral therapeutic modalities (e.g., cognitive-behavioral therapy for neurobiological conditions or EMDR therapy for BPD patients), or missed opportunities for early intervention during critical developmental periods (Shortliffe & Sepúlveda, 2018).

Second, professional liability and clinical practice standards established by professional organizations including the American Psychological Association, American Psychiatric Association, and American Medical Association require that diagnostic and treatment decisions be based on scientifically valid, transparent, and explainable evidence (APA, 2017; AMA, 2020).

Clinicians bear legal and ethical responsibility for all diagnostic and treatment decisions, creating liability concerns when recommendations are based on unexplained AI outputs that cannot be clinically justified or defended.

The *black-box* nature of many advanced AI systems, particularly deep learning architectures, creates untenable situations where clinicians must choose between utilizing potentially superior AI capabilities and maintaining professional standards for evidence-based practice. XAI systems resolve this tension by providing transparent explanations that enable clinicians to evaluate AI recommendations against their clinical knowledge, identify potential errors or biases, and integrate AI insights with comprehensive patient assessments (Cabitza et al., 2017; Tonekaboni et al., 2019).

Third, the principles of evidence-based medicine require that clinical interventions be supported by transparent, replicable, and scientifically valid evidence that can be evaluated, criticized, and improved through peer review and scientific discourse (Sackett et al., 1996). AI systems that operate as *black boxes* fundamentally violate these principles by generating recommendations through processes that cannot be examined, validated, or refined by the clinical and scientific community.

Causal AI becomes particularly important for evidence-based medicine because it enables understanding of mechanistic pathways through which interventions affect outcomes, supporting rational treatment selection and optimization. For behavioral phenotype applications, causal understanding enables clinicians to target specific endophenotype deficits (e.g., motor inhibition training for high GNG_CE presentations) rather than applying generic treatments based on superficial symptomatic patterns (Hernán, 2018; Hill, 1965).

Fourth, algorithmic bias must be minimized and health equity maximized. XAI systems provide essential capabilities for identifying and mitigating algorithmic biases that could perpetuate or exacerbate health disparities across demographic groups. Historical biases in diagnostic practices, cultural differences in symptom expression, and differential access to specialized assessments could be inadvertently encoded into AI training data, leading to systematic misclassifications for underrepresented populations (Chen et al., 2019; Rajkomar et al., 2018).

Explainable AI enables detection of these biases by revealing when model decisions rely inappropriately on demographic characteristics, socioeconomic indicators, or culturally specific presentation patterns rather than genuine neurobiological markers. For Framework B applications from the findings of this study, informed by the rich demographic data collected from the large participant sample (see Chapter 4), XAI analysis could reveal whether models inappropriately weight cultural factors in attention regulation assessments or exhibit gender biases in motor impulsivity classifications, enabling corrective interventions to ensure equitable diagnostic accuracy across diverse populations (Barocas et al., 2019; Mehrabi et al., 2021).

FDA Software as Medical Device (SaMD) Requirements. The regulatory landscape for AI/ML-based medical devices has evolved rapidly as healthcare AI applications have proliferated, with the FDA establishing comprehensive frameworks that directly impact the development and deployment of behavioral phenotype modeling systems. Understanding these requirements is essential for translating research frameworks into clinically deployable systems that meet regulatory standards while maintaining scientific rigor and clinical utility. The FDA's regulatory framework for Software as Medical Device represents the primary compliance pathway for AI-enabled clinical decision support systems in the United States. These

requirements establish mandatory standards for safety, effectiveness, and transparency that directly impact the design and deployment of behavioral phenotype modeling systems.

Understanding these regulatory requirements is essential for translating research prototypes into clinically deployable systems that meet legal and safety standards.

SaMD Classification Framework. The regulatory classification of Software as Medical Device follows risk-based categorization frameworks that evaluate both the type of healthcare decision supported and the clinical context of application (FDA, 2017; IMDRF, 2014). For neurocomputational behavioral phenotype modeling systems utilizing Framework B features, classification would be expected to fall within Class II Medical Device categories, as incorrect diagnostic classifications could lead to inappropriate treatments with significant but generally reversible clinical consequences. This classification level requires systematic development processes including comprehensive risk analysis, detailed architectural documentation, rigorous testing protocols, and ongoing post-market surveillance to ensure continued safety and effectiveness throughout the product lifecycle (FDA, 2021):

1. *Class II Medical Device Classification* encompasses software providing diagnostic support for conditions where incorrect decisions could lead to significant but generally reversible harm. For behavioral phenotype classification systems, this includes comprehensive 510(k) pre-market submissions demonstrating safety and effectiveness, quality management system compliance, and adherence to recognized consensus standards for medical device software development (FDA, 2021).
2. *Software Lifecycle Processes (IEC 62304)* establish mandatory systematic development frameworks encompassing risk assessment, architectural design documentation, implementation protocols, comprehensive testing phases, and

- continuous post-market monitoring. Ensemble digital twin architectures must maintain detailed documentation covering individual component specifications, integration methodologies, training datasets and procedures, validation study results, and real-time performance tracking systems throughout deployment (IEC, 2015).
3. *Clinical Evaluation Requirements* mandate that AI/ML-enabled medical devices demonstrate clinical effectiveness through rigorously designed validation studies examining real-world performance metrics, clinical utility measures, and comprehensive safety assessments. Framework B applications require prospective clinical investigations establishing that AI-enhanced diagnostic processes produce superior patient outcomes relative to conventional assessment methodologies (FDA, 2021).
 4. *Algorithm Change Control Plans* constitute specialized regulatory protocols for adaptive AI/ML systems maintaining learning capabilities post-deployment. Regulatory compliance demands pre-established frameworks for continuous algorithm monitoring, performance degradation detection, systematic update implementation, and modification validation while preserving patient safety standards. Ensemble digital twin architectures require integrated change control capabilities from initial development phases rather than subsequent retrofitting approaches (FDA, 2021).

Risk Management and Quality Management Systems. ISO 14971 (an international standard for medical devices) risk management standards mandate comprehensive hazard identification, assessment, and control processes throughout medical device lifecycles (ISO,

2019). Behavioral phenotype neurocomputational AI systems would require systematic risk evaluation across multiple operational domains:

1. *Clinical Risks* encompass misclassification errors resulting in suboptimal treatment pathways, diagnostic delays compromising intervention timing, excessive reliance on AI outputs diminishing clinical judgment, and systematic biases producing inequitable outcomes across patient populations. Mitigation frameworks must incorporate uncertainty quantification mechanisms, confidence-based recommendation thresholds, mandatory clinician oversight protocols, and systematic bias detection and correction procedures.
2. *Technical Risks* involve deteriorating data quality affecting model performance, algorithmic drift reflecting population changes, cybersecurity threats to cloud-based infrastructure, and system failures during critical clinical decision points. Risk control strategies encompass robust data integrity validation, continuous algorithmic performance surveillance, comprehensive information security protocols, and fault-tolerant system designs ensuring controlled degradation rather than abrupt failures.
3. *Operational Risks* include insufficient user training creating opportunities for misapplication, workflow integration challenges disrupting clinical processes, interface design inadequacies causing interpretation errors, and limited technical support affecting deployment success. Risk minimization requires structured competency development programs, comprehensive workflow integration analysis, human factors-informed interface design, and robust technical support infrastructure.

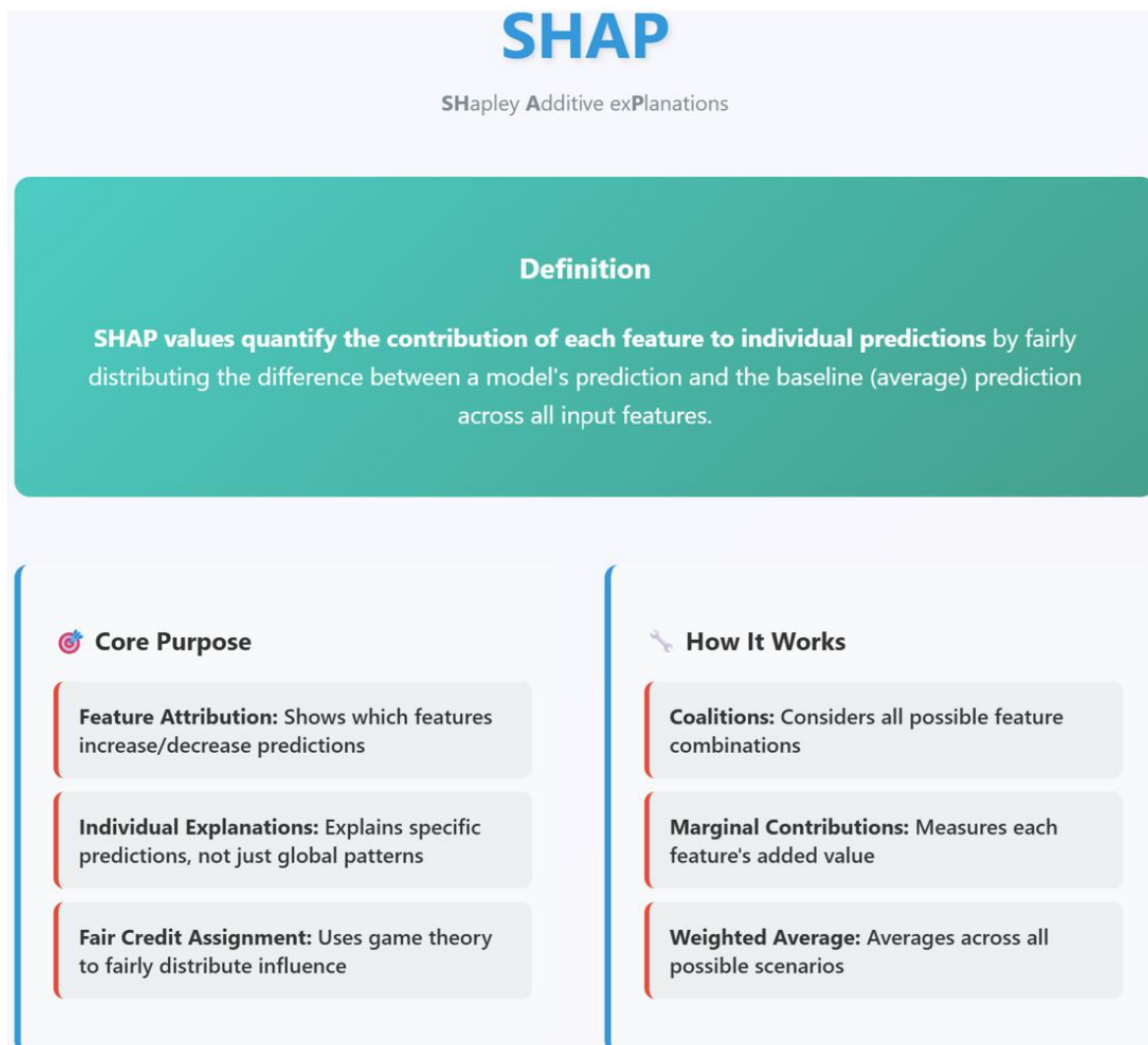
ISO 13485 quality management frameworks mandate systematic documentation and control processes covering design management, organizational responsibility, resource

allocation, product development, and continuous improvement activities (ISO, 2016). AI/ML medical device applications require comprehensive version control systems for datasets and algorithms, standardized validation procedures for software updates, complete traceability linking predictions to specific model configurations, and systematic corrective action protocols addressing identified performance deficiencies.

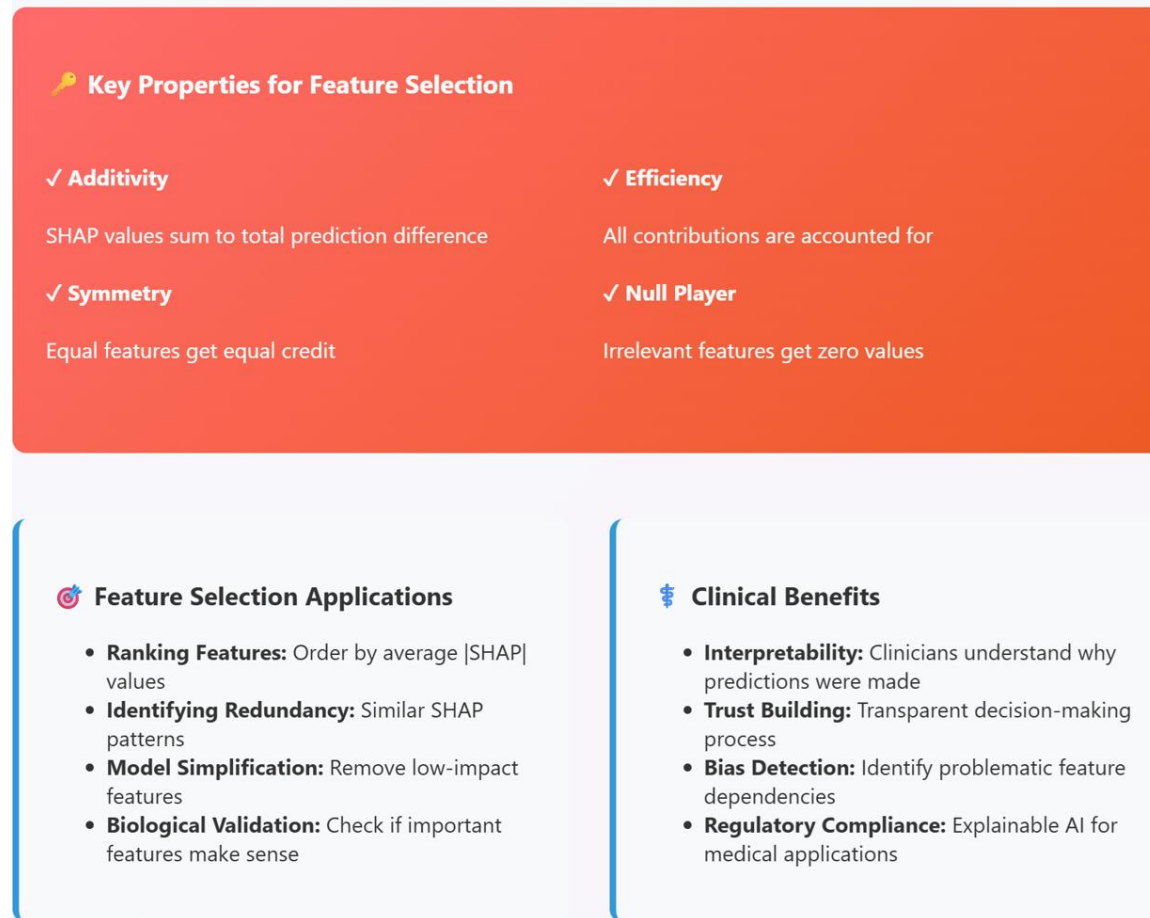
SHAP Values and Mathematical Explainability Methods.

Figure 84

Shapley Additive exPlanations (SHAP)



SHapley Additive exPlanations (SHAP) represent a unified framework for explaining the output of any *black box* machine learning model by quantifying the contribution of each feature to individual predictions (Lundberg & Lee, 2017; Shapley, 1953). SHAP values provide feature attribution by fairly distributing the difference between a model's prediction and the baseline (average) prediction across all input features, ensuring that the sum of feature contributions equals the total prediction difference (Lundberg & Lee, 2017; Shapley, 1953). The core purpose encompasses feature attribution (showing which features increase or decrease predictions), individual explanations (explaining specific predictions rather than just global patterns), and fair credit assignment (using game theory principles to fairly distribute influence across features; Lundberg & Lee, 2017; Molnar, 2020; Shapley, 1953). The mathematical foundation operates through coalitions (considering all possible feature combinations), marginal contributions (measuring each feature's added value), and weighted averaging (averaging across all possible scenarios to ensure fair attribution; Molnar, 2020).

Figure 85*SHAP Values for XAI Feature Selection*

The key properties of SHAP values ensure mathematical rigor and clinical reliability through four essential axioms (Lundberg & Lee, 2017). Additivity guarantees that SHAP values sum to the total prediction difference, ensuring complete attribution accountability. Efficiency ensures that all contributions are accounted for without missing or double-counting feature influences. Symmetry provides that equal features receive equal credit, preventing arbitrary preference assignments. The null player property ensures that irrelevant features receive zero values, maintaining logical consistency. For feature selection applications, SHAP enables

ranking features by average |SHAP| values, identifying redundancy through similar SHAP patterns, model simplification by removing low-impact features, and biological validation by checking whether important features align with clinical knowledge. Clinical benefits include interpretability (enabling clinicians to understand prediction reasoning), trust building (providing transparent decision-making processes), bias detection (identifying problematic feature dependencies), and regulatory compliance (meeting explainable AI requirements for medical applications; Adadi & Berrada, 2018; FDA, 2021).

Figure 86

SHAP Value Mathematical Implementation

$$\phi_i(f) = \sum_{S \subseteq F \setminus \{i\}} \frac{|S|! \cdot (|F| - |S| - 1)!}{|F|!} \cdot [f(S \cup \{i\}) - f(S)]$$

$$\phi_i(f) = \sum_{S \subseteq F \setminus \{i\}} \text{Weight} \times \text{Marginal Contribution}$$

Where:

$$\text{Weight} = \frac{|S|! \times (|F| - |S| - 1)!}{|F|!}$$

$$\text{Marginal Contribution} = [f(S \cup \{i\}) - f(S)]$$

Variable Definitions:

$\phi_i(f)$	SHAP value for feature i in model f
F	Complete set of all features
S	Subset of features excluding feature i
$S \subseteq F \setminus \{i\}$	S is a subset of all features except i
$ S $	Cardinality (number of elements) in subset S
$ F $	Total number of features
$f(S \cup \{i\})$	Model prediction using features in S plus feature i
$f(S)$	Model prediction using only features in subset S

The mathematical foundation of SHAP values builds upon cooperative game theory, where the Shapley value formula provides the theoretical framework for fair feature attribution (Shapley, 1953). The mathematical formula is illustrated in Figure 87, where F represents the complete set of all features, S represents any subset of features excluding feature i , $|S|$ denotes the cardinality (number of elements) in subset S , $|F|$ represents the total number of features, $f(S \cup$

$\{i\}$) represents the model prediction using features in S plus feature i , and $f(S)$ represents the model prediction using only features in subset S (Lundberg & Lee, 2017). This mathematical structure ensures that SHAP values satisfy all required axioms while providing interpretable explanations for complex model predictions in clinical applications.

With the regulatory requirements described in the previous section in mind and with reference to the ensemble digital twin architectures discussed previously that include black-box deep learning methods, the requirement for explainability of these deep learning models becomes clear. In effect, for traditional black-box deep learning architectures, SHAP values provide a mathematical proxy for explainability, effectively XAI. For behavioral phenotype modeling using Framework B features, SHAP values enable precise quantification of how NPE, GNG_CE, and SST_OE components contribute to specific behavioral phenotype classifications, supporting evidence-based clinical decision-making. Implementation of SHAP methods across different model architectures requires understanding both the theoretical foundations and practical computational considerations for clinical deployment.

Mathematical Foundation of SHAP Values. The mathematical foundation of SHAP values builds upon cooperative game theory principles, where prediction tasks are conceptualized as games with input features serving as contributing players (Lundberg & Lee, 2017). For behavioral phenotype applications using Framework B features, the SHAP value ϕ_i for any given feature i represents its average marginal contribution across all possible feature combinations. For Framework B's three-component structure (NPE, GNG_CE, SST_OE), this approach enables exact computation of feature contributions without approximation methods, providing mathematically optimal explanations for clinical decision support. For Framework B applications with three features (NPE, GNG_CE, SST_OE), this requires evaluating $2^3 = 8$

possible feature combinations to compute exact SHAP values. The computational complexity increases exponentially with feature dimensionality, necessitating approximation methods for higher-dimensional applications, but Framework B's low dimensionality enables exact computation providing mathematically optimal explanations.

Mathematical Intuition and Clinical Implementation.

Figure 87

Mathematical Intuition for SHAP Values

$\frac{|S|! \times (|F| - |S| - 1)!}{|F|!}$

The Weight Term: $\frac{|S|! \times (|F| - |S| - 1)!}{|F|!}$ represents the probability of encountering subset S when randomly ordering all features.

The Contribution Term: $[f(S \cup \{i\}) - f(S)]$ measures how much feature i changes the prediction when added to coalition S .

The Sum: We average the marginal contributions across all possible coalitions, weighted by their probability.

Example for Motor Impulsivity Prediction

Features: $F = \{\text{preservative responses, commission errors, COMT genotype}\}$

For COMT genotype SHAP value:

$$\varphi_{COMT}(f) = \sum_{S \subseteq \{\text{preservative, commission}\}} \frac{|S|! \times (2 - |S|)!}{3!} \times [\text{marginal contribution}]$$

This sums over all possible subsets: $\{\}, \{\text{preservative}\}, \{\text{commission}\}, \{\text{preservative, commission}\}$

The mathematical structure of SHAP values provides essential clinical guarantees through its weighting scheme and contribution calculations (Lundberg & Lee, 2017). The weight term $|S|! \times (|F| - |S| - 1)! / |F|!$ provides probabilistic weighting where smaller feature subsets receive higher weights due to the greater number of ways they can occur during random feature permutation (Molnar, 2020). All weights sum to unity, providing a proper probability

distribution that ensures fair attribution across all possible scenarios (Shapley, 1953). The contribution term $[f(S \cup \{i\}) - f(S)]$ measures how much feature i changes prediction when added to coalition S , providing the marginal contribution essential for understanding feature importance (Lundberg & Lee, 2017, p. 4768).

For motor impulsivity research applications using Framework B, SHAP values would fairly distribute *credit* for predictions among preservative responses (PR), commission errors (GNG_CE), and genetic factors, while accounting for all possible feature combinations. This mathematical rigor ensures that clinical explanations are mathematically sound and defensible, addressing regulatory requirements for transparent AI decision-making in healthcare applications (FDA, 2021).

Implementation Considerations and Clinical Deployment.

Figure 88

Practical Mathematical Implementation of SHAP Values

Key Mathematical Components

Weight Interpretation:

- **Numerator:** $|S|! \times (|F| - |S| - 1)!$ counts the number of ways to order features
- **Denominator:** $|F|!$ gives total possible orderings
- **Result:** Probability of encountering subset S in random feature ordering

Marginal Contribution: $[f(S \cup \{i\}) - f(S)]$ shows exactly how much feature i adds when included

Why This Mathematical Structure Matters

The fraction $|S|! \times (|F| - |S| - 1)! / |F|!$ ensures that:

1. **Smaller coalitions get more weight** (there are more ways to encounter them)
2. **All weights sum to 1** (proper probability distribution)
3. **Fair attribution** across all possible scenarios

For motor impulsivity (dopaminergic disinhibition) research, this means SHAP values will fairly distribute the "credit" for predictions among preservative responses, commission errors, genetic factors, etc., while accounting for all possible combinations of these features.

The mathematical rigor ensures that clinical explanations are not just intuitive, but mathematically sound and defensible (i.e., interpretable and explainable)!

Practical mathematical implementation requires understanding the computational trade-offs between different SHAP approaches (Lundberg et al., 2020). Exact calculation remains feasible only for small feature sets (typically <15 features), making it suitable for Framework B's three-component structure but requiring approximation methods for more complex multimodal applications (Molnar, 2020). TreeSHAP provides substantial computational advantages for tree-based models, while the SHAP library offers optimized implementations across different model architectures (Lundberg et al., 2020).

Figure 89

Computational Efficient Implementation of SHAP Values in Python (Exact vs. Approximate)



Figure 89 provides screen shots of Python code (Panel 1, exact method; Panel 2, approximation method) illustrating the contrast of efficiently implementing SHAP values. Key implementation considerations include exact calculation limitations (computationally expensive), approximation method (more practical and computationally efficient) necessity for realistic datasets, selection of background data (often using the mean or median of the training set), and

model-specific optimizations where LinearSHAP and TreeSHAP provide substantially faster computational performance than general KernelSHAP approaches do (Lundberg et al., 2020). The choice of background data proves crucial, as it defines the baseline against which feature contributions are measured, directly affecting the magnitude and interpretation of SHAP values in clinical contexts (Molnar, 2020, p. 181).

Figure 90

Recommended Python SHAP Value Implementation

3. Using the SHAP Library (Recommended)

```
import shap
import pandas as pd

# For motor impulsivity prediction
def explain_motor_impulsivity_prediction(model, patient_data, background_data):
    """
    Explain motor impulsivity prediction using SHAP
    """
    # Choose appropriate explainer based on model type
    if hasattr(model, 'predict_proba'): # Tree-based
        explainer = shap.TreeExplainer(model)
    else: # Model-agnostic
        explainer = shap.KernelExplainer(model.predict, background_data)

    # Calculate SHAP values
    shap_values = explainer.shap_values(patient_data)

    # For binary classification, use positive class
    if len(shap_values) == 2:
        shap_values = shap_values[1]

    return shap_values

# Example usage for recommended future research
feature_names = ['preservative_responses', 'commission_errors', 'COMT_genotype',
                 'stop_signal_RT', 'working_memory']

# Calculate explanations
shap_vals = explain_motor_impulsivity_prediction(trained_model, patient_features,
                                                background_features)

# Clinical interpretation
explanation = pd.DataFrame({
    'Feature': feature_names,
    'SHAP_Value': shap_vals,
    'Interpretation': ['Increases impulsivity risk' if val > 0
                      else 'Decreases impulsivity risk' for val in shap_vals]
})

print(explanation)
```

Key Implementation Considerations:

- **Exact calculation:** Only feasible for small feature sets (< 15 features)
- **Approximation methods:** Necessary for realistic datasets
- **Background data:** Crucial choice - often uses training set mean or median
- **Model-specific optimizations:** [TreeSHAP](#), [LinearSHAP](#) much faster than general [KernelSHAP](#)

The beauty of SHAP is that regardless of implementation method, the values always satisfy the mathematical properties, making them reliable for clinical explanations!

Figure 90 provides a screenshot of Python code illustrating a recommended implementation for future research. The most significant advantage of SHAP lies in its mathematical rigor, efficiency, and guarantees. Regardless of implementation method, SHAP

values are engineered to consistently satisfy the essential mathematical properties of efficiency, symmetry, dummy feature, and additivity (Lundberg & Lee, 2017). This consistency makes SHAP values reliable for clinical explanations across different model architectures and neurocomputational approaches, providing the theoretical foundation necessary for regulatory compliance and professional liability protection in healthcare AI applications (FDA, 2021).

SHAP Variants for Different Model Types. TreeSHAP provides efficient computation of SHAP values for tree-based ensemble methods including random forests, gradient boosting, and XGBoost models that might serve as baseline comparisons for neural network approaches. TreeSHAP exploits the tree structure to compute exact SHAP values in polynomial time rather than exponential time required for model-agnostic approaches (Lundberg et al., 2020).

For random forest baselines in ensemble digital twin architectures, TreeSHAP would reveal how Framework B components are weighted across different trees and how feature interactions contribute to final predictions. This provides interpretable comparisons with more complex neural network explanations, enabling validation of explanation consistency across different modeling approaches.

DeepSHAP extends SHAP to deep neural networks by leveraging backpropagation algorithms to efficiently compute feature attributions through complex network architectures. DeepSHAP decomposes predictions through network layers, revealing how Framework B features are transformed and combined through hidden representations to generate final phenotype classifications (Lundberg & Lee, 2017).

For the MLPNN schizophrenia classification architecture, for example, DeepSHAP would trace how NPE, GNG_CE, and SST_OE values propagate through hidden layers, revealing intermediate representations and their contributions to final schizophrenia probability

outputs. This enables understanding of whether the network learns clinically interpretable feature combinations or relies on spurious statistical patterns.

Integrated gradients (IGs) provide an alternative attribution method that satisfies important mathematical axioms including sensitivity (non-contributing features receive zero attribution) and implementation invariance (identical networks receive identical attributions regardless of implementation details). Integrated gradients compute attributions by integrating gradients along a straight-line path from a baseline input to the actual input (97)

$$IG_i(x) = (x_i - x'_i) \times \int_0^1 \frac{\partial f(x' + \alpha(x - x'))}{\partial x_i} d\alpha$$

where $IG_i(x)$ represents the integrated gradient for feature i , x represents the actual input, x' represents the baseline input (typically zeros), and the integral is computed numerically using discrete approximation (Sundararajan et al., 2017).

Clinical Applications of SHAP Analysis. SHAP values enable several critical clinical applications that enhance diagnostic accuracy and treatment planning for behavioral phenotypes: (a) individual case analysis provides patient-specific explanations showing why particular behavioral phenotype classifications were assigned based on Framework B profiles. For example, a participant classified as ADHD might receive SHAP explanations showing that high GNG_CE (motor inhibition deficits) contributed +0.3 to ADHD probability, moderate SST_OE (attention regulation deficits) contributed +0.2, while normal NPE (cognitive flexibility) contributed -0.1, resulting in a net positive ADHD classification; (b) population-level pattern discovery aggregates SHAP values across large samples to identify systematic relationships between Framework B components and phenotype classifications. By way of example, this analysis could reveal that schizophrenia classifications consistently show large positive SHAP

values for all three Framework B components, while ASD classifications show mixed patterns with high NPE contributions, but variable GNG_CE and SST_OE contributions, reflecting the dimensional nature of autism spectrum presentations; (c) bias detection and mitigation employs SHAP analysis to identify inappropriate reliance on demographic characteristics or culturally specific factors rather than genuine neurobiological markers. If SHAP analysis reveals that models inappropriately weight age, gender, or socioeconomic status in behavioral phenotype classifications, for example, corrective training procedures can be implemented to ensure fair and accurate diagnostic decisions across diverse populations; (d) treatment response prediction leverages SHAP values to identify which Framework B components, for example, most strongly predict treatment responsiveness, enabling personalized intervention selection. For instance, if SHAP analysis reveals that SST_OE (attention regulation) deficits strongly predict stimulant medication responsiveness in ADHD, while GNG_CE (motor inhibition) deficits predict behavioral intervention responsiveness, clinicians can optimize treatment selection based on individual deep endophenotype profiles.

The clinical applications of SHAP analysis directly leverage the empirical discovery in Chapter 4 that multiple framework combinations provide statistically significant but differentially optimized discrimination patterns across behavioral presentations. Individual case analysis can reveal how Framework B's three feature optimal power-parsimony balance components (NPE, GNG_CE, SST_OE) capture the most robust discrimination patterns, while alternative frameworks (e.g., Framework A's [Optimal Performance] five feature combination providing the largest effect size, partial $\eta^2 = .046$) may provide superior explanations for specific clinical presentations or demographic subgroups. Population-level pattern discovery can validate whether different frameworks reveal distinct aspects of behavioral control (BRI) dysfunction,

with SHAP analysis enabling identification of optimal framework selection based on individual presentation patterns rather than applying uniform dimensional reduction assumptions. This framework flexibility addresses the fundamental limitation of traditional approaches that force complex, multidimensional constructs into single measurement paradigms, enabling neurocomputational AI systems to adapt their analytical approach based on the specific discriminative requirements of individual clinical cases while maintaining the reductionist precision necessary for mechanistic understanding.

Model-Agnostic Interpretability Methods. While SHAP values provide mathematically optimal explanations, model-agnostic interpretability methods offer complementary approaches that can provide insights into model behavior without requiring access to internal model parameters or architectures. These methods are particularly valuable for ensemble digital twin models and systems where component models may employ different architectures and mathematical frameworks. Model-agnostic interpretability methods provide essential complementary approaches to SHAP analysis, offering alternative perspectives on model behavior that can validate and enhance explanation quality. These methods are particularly valuable for ensemble digital twin models and systems where multiple model types must be integrated while maintaining consistent interpretability standards. The following approaches represent the most clinically relevant model-agnostic techniques for behavioral phenotype applications.

LIME (Local Interpretable Model-agnostic Explanations). LIME generates explanations by learning local linear approximations around specific predictions, providing interpretable explanations that approximate complex model behavior in the vicinity of individual data points (Ribeiro et al., 2016). For Framework B applications, LIME would generate linear

explanations showing how small changes in NPE, GNG_CE, or SST_OE values would affect behavioral phenotype classification probabilities.

The mathematical foundation of LIME involves optimizing a local linear model that minimizes prediction differences while maximizing interpretability

$$\text{explanation}(x) = \operatorname{argmin}_{g \in G} L(f, g, \pi_x) + \Omega(g) \quad (98)$$

where g represents the interpretable linear model, G represents the class of interpretable models, L represents the loss function measuring fidelity between the complex model f and simple model g , π_x represents a proximity measure defining the local neighborhood around x , and $\Omega(g)$ represents a penalty for model complexity (Ribeiro et al., 2016).

Attention Mechanisms for Sequential Models. For temporal applications including HMM-based BPD state transition modeling and transformer-based sequential pattern analysis, attention mechanisms provide inherent interpretability by revealing which time points or input features receive greatest focus during prediction generation. Attention weights can be visualized as heatmaps showing temporal patterns of focus across Framework B measurement sequences.

The attention interpretation for BPD state transition models would reveal which historical Framework B patterns most strongly influence current state predictions, enabling clinicians to understand temporal dependencies in emotional regulation cycles. High attention weights on recent SST_OE (attention regulation) measurements might indicate that current attention deficits strongly predict impending dysregulation episodes, supporting targeted early intervention strategies.

Feature Importance Ranking via Permutation Tests. Permutation importance provides model-agnostic measurement of feature importance by evaluating prediction degradation when individual features are randomly shuffled, destroying their relationship with target variables

while preserving marginal distributions (Breiman, 2001; Fisher et al., 2019). For Framework B applications, permutation importance would rank NPE, GNG_CE, and SST_OE components by their contribution to behavioral phenotype classification accuracy.

The permutation importance for feature i is computed as

$$PI_i = S - S\pi_i \quad (99)$$

where S represents the original model performance score, $S\pi_i$ represents the performance score after permuting feature i , and higher values indicate greater feature importance (Fisher et al., 2019). This approach provides model-agnostic importance rankings that can validate SHAP-based explanations and identify potential feature redundancies or interactions.

Regulatory Compliance for Clinical Deployment. Achieving regulatory compliance for XAI-enabled behavioral phenotype neurocomputational clinical modeling systems requires systematic integration of interpretability methods with comprehensive validation and monitoring frameworks. The regulatory landscape demands ongoing demonstration of safety, effectiveness, and explanation quality throughout the entire product lifecycle, extending far beyond initial deployment approval. These compliance requirements shape both technical implementation decisions and operational procedures for clinical AI systems.

Documentation and Validation Requirements. FDA guidance requires comprehensive documentation of AI/ML model development processes, including training data characteristics, model architecture specifications, validation methodologies, and performance metrics across diverse populations (FDA, 2024). For XAI systems, this documentation must extend to interpretability method validation, explanation accuracy assessment, and user comprehension studies demonstrating that clinicians can correctly interpret and act upon AI-generated explanations.

Explanation validation protocols must demonstrate that SHAP values, LIME explanations, and attention weights accurately reflect genuine model decision processes rather than post-hoc rationalizations that could mislead clinicians. This requires systematic comparison of explanation consistency across different interpretability methods, evaluation of explanation stability across similar inputs, and validation that explanation-guided interventions produce expected clinical outcomes.

Post-Market Surveillance and Continuous Monitoring. Regulatory compliance extends beyond initial deployment to require ongoing monitoring of AI system performance, explanation quality, and clinical outcomes throughout the product lifecycle. For behavioral phenotype neurocomputational modeling systems, this would include tracking diagnostic accuracy across demographic groups, monitoring explanation consistency over time, detecting model drift or degradation, and evaluating real-world clinical utility compared to validation study results.

Automated monitoring systems must track key performance indicators including prediction accuracy, explanation fidelity, user confidence in AI recommendations, clinical decision concordance with AI suggestions, and patient outcome improvements attributable to AI assistance. Significant deviations from expected performance patterns trigger regulatory reporting requirements and may necessitate model updates or temporary suspension of automated recommendations pending investigation and remediation.

The integration of explainable AI methods with regulatory compliance frameworks creates a foundation for responsible deployment of behavioral phenotype neurocomputational modeling systems that enhance clinical decision-making while maintaining the transparency, accountability, and safety standards essential for patient care and professional practice. Further, while the establishment of comprehensive explainable AI frameworks and regulatory compliance

protocols provides the necessary foundation for responsible AI deployment, the ultimate measure of success lies in effective, practical, and pragmatic translation to clinical practice. The progression from mathematically sophisticated, regulatory-compliant AI systems to tools that enhance real-world patient care requires systematic attention to implementation science principles, organizational change management, and human factors engineering. Even the most advanced ensemble digital twin architectures with optimal explainability features will fail to improve clinical outcomes without careful integration into existing healthcare workflows, comprehensive clinician training programs, and robust performance monitoring systems. The complexity of behavioral phenotype assessment, combined with the intricate nature of AI-assisted decision-making, creates unique challenges for clinical implementation that extend beyond traditional health information technology deployment strategies, requiring mapping historical clinical implementation standards onto novel neurocomputational AI models and systems.

Clinical Translation and Implementation of Neurocomputational Applications

This penultimate subsection of Chapter 5 on neurocomputational AI recommendations for future research focuses on translating the empirical findings from Chapter 4 for this study and suggested theoretic AI model architectures from this Chapter 5 to practical and pragmatic AI assisted behavioral phenotype clinical assessment and implementation. The progression begins with Clinical Workflow Integration Strategies, examining how ensemble digital twin architectures would be embedded within existing diagnostic processes, from initial screening through treatment planning, including seamless Electronic Health Record (EHR) integration and comprehensive Quality Assurance (QA) protocols. The discussion then advances to Clinician Training and Competency Development, addressing the essential educational frameworks needed

to prepare healthcare professionals for effective human-AI collaboration, encompassing Core Competency requirements, Multi-Modal Training approaches, and ongoing Competency Assessment and Maintenance protocols. Next, Evidence Generation and Real-World Validation outlines the systematic research methodologies required to demonstrate clinical effectiveness through Prospective Clinical Studies, Implementation Science Frameworks, and comprehensive Health Economic Evaluations that support policy decisions regarding AI technology adoption. The subsection concludes with Limitations and Future Directions, acknowledging current technical and clinical constraints while identifying priority areas for continued research and development, including multimodal RDoC integration, causal modeling approaches, federated learning frameworks, and personalized AI applications that can advance the field toward more sophisticated and clinically meaningful behavioral phenotype modeling systems.

The successful translation of ensemble digital twin architectures and explainable AI frameworks from research prototypes to clinical practice requires systematic consideration of implementation challenges, workflow integration strategies, and organizational change management processes (Damschroder et al., 2009; Proctor et al., 2011). Clinical translation encompasses not only technical deployment considerations but also comprehensive training programs, performance monitoring systems, and evidence generation protocols that demonstrate real-world clinical utility and safety (Curran et al., 2012; Glasgow et al., 2019). The complex nature of behavioral phenotype neurocomputational modeling systems necessitates multifaceted implementation approaches that address technological, organizational, and human factors challenges while maintaining the interpretability and regulatory compliance standards established in the XAI framework (Benda et al., 2020; Price et al., 2018).

Clinical Workflow Integration Strategies. The integration of AI-enabled behavioral phenotype neurocomputational modeling systems into existing clinical workflows requires careful analysis of current diagnostic processes, identification of optimal intervention points, and systematic redesign of clinical procedures to leverage AI capabilities while preserving essential human oversight and clinical judgment (Karsh et al., 2010; Sockolow et al., 2012). Successful workflow integration must balance efficiency gains from AI assistance with maintenance of clinical standards, professional autonomy, and patient-centered care principles (Beam & Kohane, 2018; Topol, 2019).

Assessment and Diagnostic Workflow Modification. Current behavioral phenotype assessment workflows typically involve multiple stages including initial screening, comprehensive evaluation, differential diagnosis, and treatment planning phases that could be enhanced through strategic AI integration points (Achenbach & Rescorla, 2001; Mash & Hunsley, 2005). The Framework B assessment protocol would be integrated early in the evaluation process, providing standardized deep endophenotype measurements that serve as validated inputs for ensemble digital twin analysis (Cuthbert & Insel, 2013; Morris & Cuthbert, 2012).

Initial screening phases could incorporate rapid Framework B assessment through tablet-based cognitive and behavioral tasks administered in waiting areas or during intake procedures, generating preliminary deep endophenotype profiles that inform subsequent evaluation priorities (Bauer et al., 2014; Faurholt-Jepsen et al., 2013). Comprehensive evaluation phases would expand Framework B assessment to include full test batteries while ensemble digital twin systems process real-time data to generate provisional behavioral phenotype classifications and uncertainty estimates (Huibers et al., 2015; Jacobson & Truax, 1991).

Differential diagnosis phases represent the most critical AI integration points, where ensemble predictions, SHAP explanations, and uncertainty quantifications support clinical decision-making without replacing professional judgment (Bates et al., 2003; Garg et al., 2005). Clinicians would receive comprehensive AI-generated reports including behavioral phenotype probability distributions, confidence intervals, feature importance rankings, and evidence summaries that inform diagnostic reasoning while maintaining final decision authority (Sittig & Singh, 2012; Wright et al., 2011).

Treatment planning phases leverage AI insights to optimize intervention selection based on predicted treatment responsiveness derived from individual behavioral endophenotype profiles (DeRubeis et al., 2014; Lutz et al., 2006). The system would provide evidence-based recommendations for therapeutic modalities, medication considerations, and monitoring protocols while enabling clinician modification based on additional clinical factors not captured in Framework B assessments (Kazdin, 2007; Weisz et al., 2013).

Electronic Health Record (EHR) Integration. Seamless integration with existing EHR systems represents a critical requirement for clinical adoption, necessitating comprehensive data exchange protocols, standardized terminology mappings, and workflow automation capabilities that minimize administrative burden while maximizing clinical utility (Boonstra & Broekhuis, 2010; Kruse et al., 2016). Framework B assessments and AI-generated insights would need to be integrated into clinical documentation systems with appropriate version control, audit trails, and decision support alerts (Ash & Bates, 2005; Shortliffe & Cimino, 2006).

Technical integration requires development of HL7 FHIR (Fast Healthcare Interoperability Resources)-compliant (a standard for exchanging healthcare information under Health Level Seven International; HL7, 2023) APIs that enable bidirectional data exchange

between AI systems and EHR platforms, ensuring that Framework B measurements, ensemble predictions, and explanation summaries are automatically populated into appropriate clinical documentation templates (Dolin et al., 2006; Mandel et al., 2016). Standardized terminology mappings ensure consistent representation of deep endophenotype measurements and behavioral phenotype classifications across different EHR vendors and clinical settings (Chute et al., 1996; Rosenbloom et al., 2006).

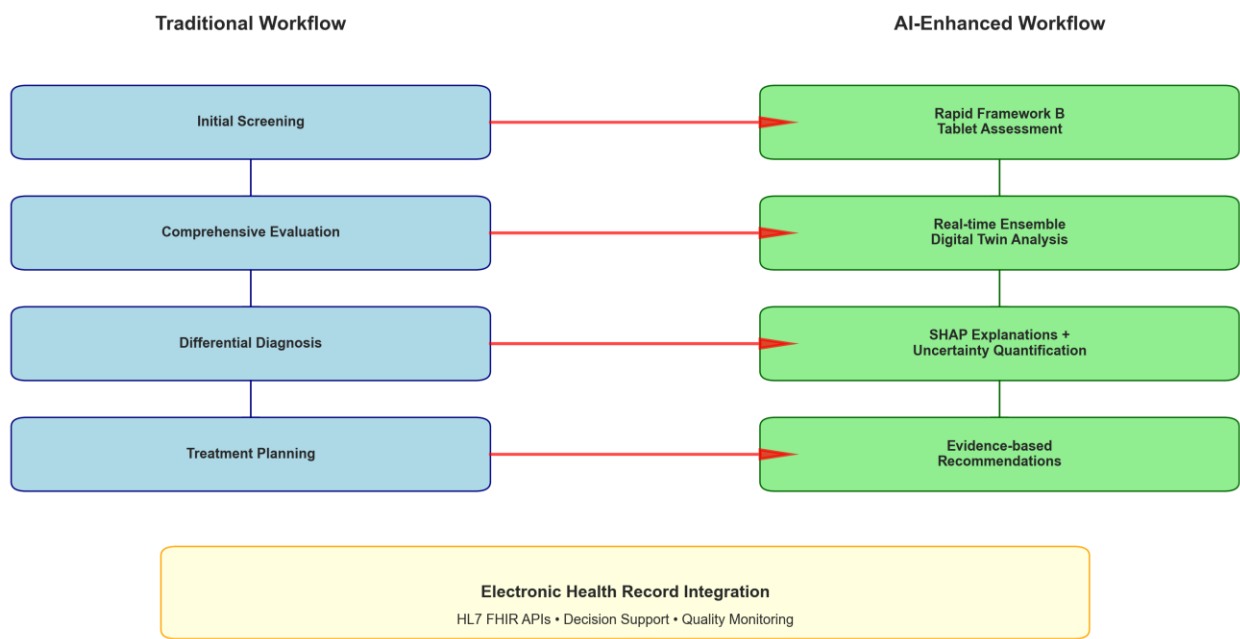
Clinical decision support integration would provide real-time alerts and recommendations based on ensemble digital twin analysis, with configurable threshold settings that balance sensitivity and specificity based on clinical context and user preferences (Bright et al., 2012; Kawamoto et al., 2005). Alert fatigue mitigation requires careful calibration of notification triggers, prioritization of high-confidence recommendations, and user customization options that adapt to individual clinician preferences and practice patterns (Ancker et al., 2017; Phansalkar et al., 2010).

Quality Assurance and Performance Monitoring. Clinical implementation requires comprehensive quality assurance protocols that monitor AI system performance, identify potential errors or biases, and ensure continued accuracy and safety throughout deployment (Cabitza et al., 2017; Floridi et al., 2018). Performance monitoring systems must track multiple dimensions including prediction accuracy, explanation fidelity, user satisfaction, clinical utility, and patient outcomes across diverse populations and clinical settings (Davis et al., 2020; Liu et al., 2020).

Real-time monitoring dashboards provide clinicians and administrators with continuous visibility into system performance metrics, including diagnostic accuracy rates, confidence distributions, explanation consistency scores, and user engagement patterns (Sendak et al., 2020;

Shah et al., 2019). Automated anomaly detection algorithms identify unusual patterns in AI behavior, unexpected changes in prediction distributions, or degradation in explanation quality that might indicate technical problems or dataset drift requiring intervention (Davis et al., 2017; Finlayson et al., 2021).

Figure 91
Clinical Workflow Integration Framework



Note: Illustrates the transformation from traditional diagnostic workflows to AI-enhanced processes with Framework B integration points, ensemble digital twin outputs, and comprehensive EHR integration.

Periodic validation studies would compare AI-assisted diagnostic decisions with expert consensus standards, evaluating not only accuracy metrics, but also the clinical appropriateness of AI recommendations and the effectiveness of explanatory information in supporting clinical reasoning (Keane & Topol, 2018; Rajpurkar et al., 2017). These studies inform ongoing model

refinement, training program updates, and workflow optimization initiatives that enhance clinical utility while maintaining safety standards (Chen et al., 2019; Obermeyer et al., 2019). While technical integration represents the foundational requirement for clinical deployment, successful implementation depends critically on comprehensive clinician preparation and competency development that ensures safe and effective human-AI collaboration.

Clinician Training and Competency Development. Successful clinical implementation requires comprehensive training programs that develop clinician competencies in AI-assisted diagnostic reasoning, interpretation of ensemble predictions and SHAP explanations, and appropriate integration of AI insights with clinical expertise (Masters, 2019; Wartman & Combs, 2018). Training programs must address both technical understanding of AI capabilities and limitations as well as practical skills for effective human-AI collaboration in clinical decision-making contexts (Crigger et al., 2022; Paranjape et al., 2019).

Core Competency Framework. Essential competencies for AI-assisted behavioral phenotype assessment include understanding of ensemble digital twin architectures, interpretation of probabilistic predictions and uncertainty estimates, evaluation of SHAP-based feature attributions, and recognition of potential biases or limitations in AI recommendations (Matheny et al., 2020; McCoy et al., 2020). Clinicians must develop skills in translating AI insights into clinical action plans while maintaining appropriate skepticism and independent clinical judgment (Babic et al., 2021; Shortliffe & Sepúlveda, 2018).

Technical competencies encompass understanding of Framework B endophenotype measurements and their clinical significance, interpretation of ensemble prediction confidence intervals and their implications for diagnostic certainty, evaluation of SHAP value magnitudes and directions for individual cases, and recognition of situations where AI recommendations may

be unreliable or inappropriate for clinical application (Holzinger et al., 2017; Murdoch et al., 2019).

Clinical integration competencies include skills in combining AI insights with traditional assessment information, communicating AI-derived diagnostic impressions to patients and families, documenting AI-assisted decision-making processes in clinical records, and recognizing when additional evaluation or domain expert consultation is indicated despite AI recommendations (Lysaght et al., 2019; Price et al., 2019).

Multi-Modal Training Approaches. Effective training programs would employ diverse pedagogical approaches including didactic education, case-based learning, simulation exercises, and supervised clinical application with domain expert feedback (Cook et al., 2008; Issenberg et al., 2005). Didactic components would provide foundational understanding of AI principles, ensemble architectures, and explainability methods relevant to behavioral phenotype applications (Pusic et al., 2012; Ritter et al., 2017).

Case-based learning would utilize anonymized clinical vignettes with actual Framework B data and AI-generated explanations, enabling clinicians to practice interpretation skills and diagnostic reasoning in realistic scenarios without patient risk (Thistlethwaite et al., 2012; Williams, 2005). Interactive exercises would allow manipulation of Feature B values to observe corresponding changes in ensemble predictions and SHAP attributions, developing intuitive understanding of model behavior and limitations (McLean, 2016; Ruiz Moral, 2019).

Simulation environments provide safe opportunities to practice human-AI collaboration skills, including scenarios with conflicting AI and clinical impressions, cases with high uncertainty requiring additional evaluation, and situations where AI explanations reveal unexpected patterns requiring clinical investigation (McGaghie et al., 2010; Motola et al., 2013). Supervised clinical

application with domain expert mentorship would enable gradual competency development in real patient care contexts while ensuring patient safety and optimal outcomes (Dornan et al., 2007; Kilminster & Jolly, 2000).

Competency Assessment and Maintenance. Historically adapted systematic competency assessment protocols would evaluate clinician proficiency in AI-assisted diagnostic reasoning through multiple assessment modalities including written examinations, case interpretation exercises, and direct observation of clinical practice (Miller, 1990; van der Vleuten, 1996). Assessment standards would ensure consistent competency levels across different practitioners and clinical settings while identifying individuals requiring additional training or support (Holmboe et al., 2010; Norcini et al., 2011).

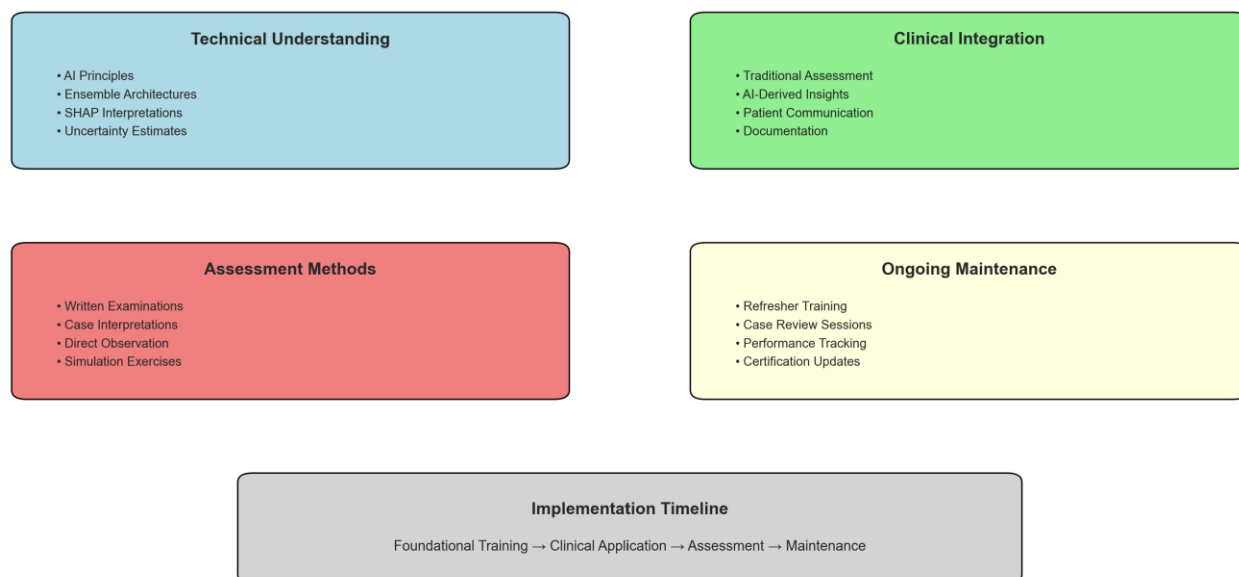
Written assessments evaluate understanding of AI principles, interpretation of probabilistic outputs, and knowledge of appropriate clinical applications and limitations (Downing, 2003; Schuwirth & van der Vleuten, 2011). Case-based assessments measure practical skills in integrating AI insights with clinical information, generating appropriate diagnostic impressions, and developing evidence-based treatment plans incorporating AI recommendations (Case & Swanson, 2001; Swanson et al., 1995).

Ongoing competency maintenance would require periodic refresher training, participation in case review sessions, and demonstration of continued proficiency through regular assessment activities (Davis et al., 1999; Eva, 2007). Competency tracking systems would monitor individual practitioner performance, identify areas requiring additional training, and ensure maintenance of certification standards throughout the practitioner's career (Levinson et al., 2010; Peck et al., 2000). Beyond individual clinician competency, widespread clinical adoption

requires systematic evidence generation that demonstrates real-world effectiveness and supports institutional and policy-level decision-making regarding AI technology investments.

Figure 92

Clinician Competency Development Framework



Evidence Generation and Real-World Validation. Clinical translation requires systematic evidence generation demonstrating that AI-assisted behavioral phenotype assessment improves clinical outcomes compared to standard of care approaches (Craig et al., 2008; Eccles et al., 2009). Evidence generation protocols must address multiple dimensions including diagnostic accuracy, treatment effectiveness, clinician satisfaction, patient outcomes, and cost-effectiveness across diverse clinical populations and practice settings (Godwin et al., 2003; Zwarenstein et al., 2008).

Prospective Clinical Studies. Randomized controlled clinical trials comparing AI-assisted versus standard diagnostic approaches provide the highest level of evidence for clinical

effectiveness and safety (Jadad et al., 1996; Schulz et al., 2010). Study designs must account for the complex nature of behavioral phenotype assessment, incorporating appropriate outcome measures, follow-up periods, and control conditions that reflect real-world clinical practice (Patsopoulos, 2011; Thorpe et al., 2009).

Primary outcomes focus on diagnostic accuracy improvements, measured through comparison with domain expert consensus standards or longitudinal clinical outcomes that validate initial diagnostic impressions (Bossuyt et al., 2003; Rutjes et al., 2005). Secondary outcomes include time to accurate diagnosis, treatment response rates, clinician confidence in diagnostic decisions, and patient satisfaction with assessment processes (Begg et al., 1996; Guyatt et al., 2011).

Pragmatic trial designs often embed research activities within routine clinical care, minimizing disruption to normal workflows while generating evidence under realistic implementation conditions (Schwartz & Lellouch, 1967; Thorpe et al., 2009). In such cases, cluster randomization at the clinic or provider level reduces contamination while enabling evaluation of organizational and contextual factors that influence implementation success (Campbell et al., 2004; Eldridge et al., 2012).

Implementation Science Frameworks. Implementation science methodologies provide systematic approaches for evaluating adoption, penetration, and sustainability of AI-assisted behavioral phenotype assessment in clinical practice (Eccles & Mittman, 2006; Proctor et al., 2009). Frameworks such as RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) and CFIR (Consolidated Framework for Implementation Research) can guide comprehensive evaluation of implementation processes and outcomes for neurocomputational AI assisted clinical applications. (Damschroder et al., 2009; Glasgow et al., 1999).

Reach assessments can evaluate the proportion of eligible patients and clinicians who participate in AI-assisted assessment, identifying barriers to access and strategies for improving utilization across diverse populations (Glasgow et al., 2013; Kessler et al., 2013). Effectiveness evaluations would measure clinical outcomes under real-world implementation conditions, accounting for variations in fidelity, user experience, and organizational support (Glasgow et al., 2005; Tunis et al., 2003).

Adoption analyses can examine factors influencing clinician and organizational decisions to implement AI systems, including perceived advantages, compatibility with existing workflows, complexity of implementation, and availability of technical support (Greenhalgh et al., 2004; Rogers, 2003). Implementation assessments would evaluate the fidelity of AI system deployment compared to intended protocols, identifying modifications necessary for successful integration into clinical practice (Carroll et al., 2007; Durlak & DuPre, 2008).

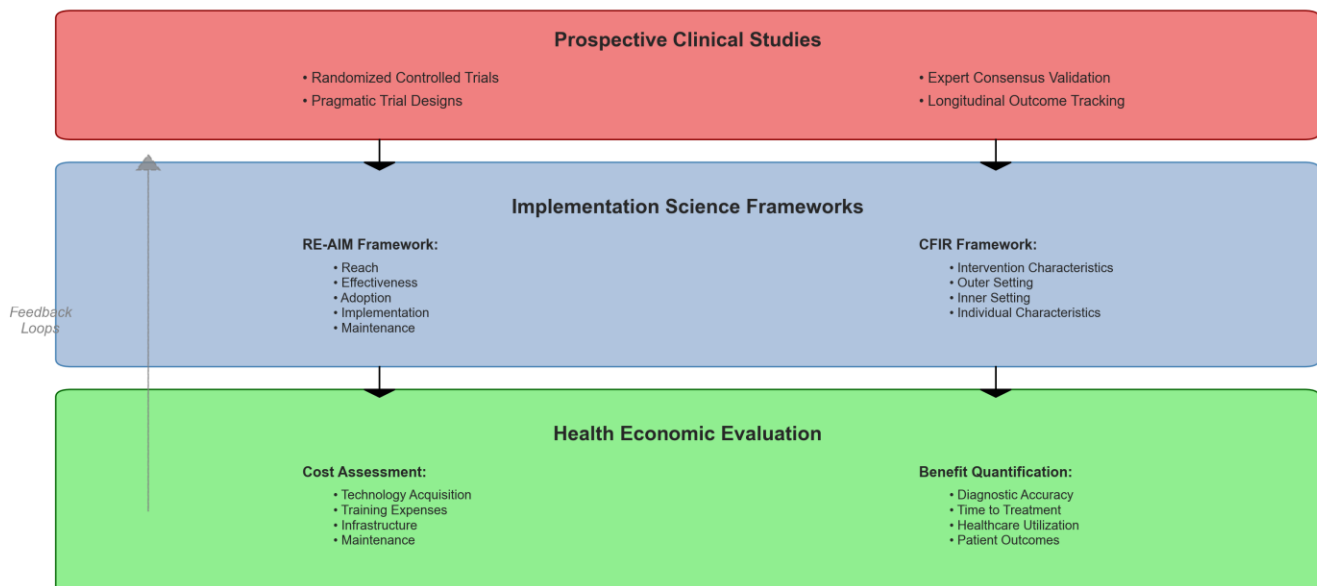
Health Economic Evaluation. Pharmacoeconomics informed cost-effectiveness analyses would enable the evaluation of the economic impact of AI-assisted behavioral phenotype assessment, comparing implementation costs with clinical benefits and healthcare utilization changes (Drummond et al., 2015; Sanders et al., 2016). Economic evaluations would account for multiple cost categories including technology acquisition, training expenses, workflow modifications, and ongoing maintenance requirements (Briggs et al., 2006; Sculpher et al., 2006).

Direct cost assessments include AI system licensing fees, hardware and infrastructure requirements, clinician training expenses, and technical support costs (Johnston et al., 2013; Karnon et al., 2012). Indirect cost considerations encompass workflow disruption during implementation, productivity changes during learning curves, and opportunity costs associated

with alternative technology investments (Brouwer et al., 1999; Larg & Moss, 2011). Benefit quantification would measure improvements in diagnostic accuracy, reductions in time to appropriate treatment, decreased need for repeat assessments or specialist referrals, and prevention of inappropriate interventions resulting from diagnostic errors (Husereau et al., 2013; Weinstein et al., 2009). Cost-effectiveness ratios would enable comparison with alternative healthcare interventions and support healthcare policy decisions regarding AI technology adoption (Neumann et al., 2014; Siegel et al., 1996). Despite the promising potential demonstrated through systematic implementation and validation approaches, current neurocomputational methods face significant limitations that must be acknowledged and addressed through continued research and development efforts.

Figure 93

Implementation Science and Evidence Generation Pipeline



Note: Illustrates the systematic research-to-practice pathway from prospective clinical studies through implementation science frameworks to comprehensive health economic evaluation, with feedback loops enabling continuous improvement.

Comprehensive Digital Twin Development and Deployment for Schizophrenia

Building upon the foundational individual model architectures, ensemble methodologies, regulatory frameworks, explainable AI requirements, and clinical implementation strategies detailed above, this final section on recommendations for future research through neurocomputational model research, development, and deployment demonstrates the integration of these concepts through a more comprehensive research proposal for a schizophrenia neurocomputational digital twin model and system. Rather than suggesting optimal architectures for specific behavioral phenotypes, the preceding discussion illustrates how model selection should align with the unique dynamics of the target condition, available data modalities, and specific research objectives (Durstewitz et al., 2019; Rasheed et al., 2020). As discussed above, ensemble approaches often provide superior performance by leveraging complementary strengths across multiple modeling paradigms (Dietterich, 2000; Zhou, 2012).

The following comprehensive digital twin example is intended to leverage the deep endophenotypes and the Frameworks discovered by this study (Framework A, B, C, D) and trait and state motor impulsivity and behavioral response inhibition (BRI) to inform and accompany (in the spirit of the Generic Model Study discussed in Chapter 2) more complex dynamical systems (invoking NDST and RDoC) comprising a plurality of interrelated feedback systems comprising candidate endophenotypes and neuropsychological constructs. The example below employs overparameterized autoencoders (OAEs) for schizophrenia modeling—contrasting with

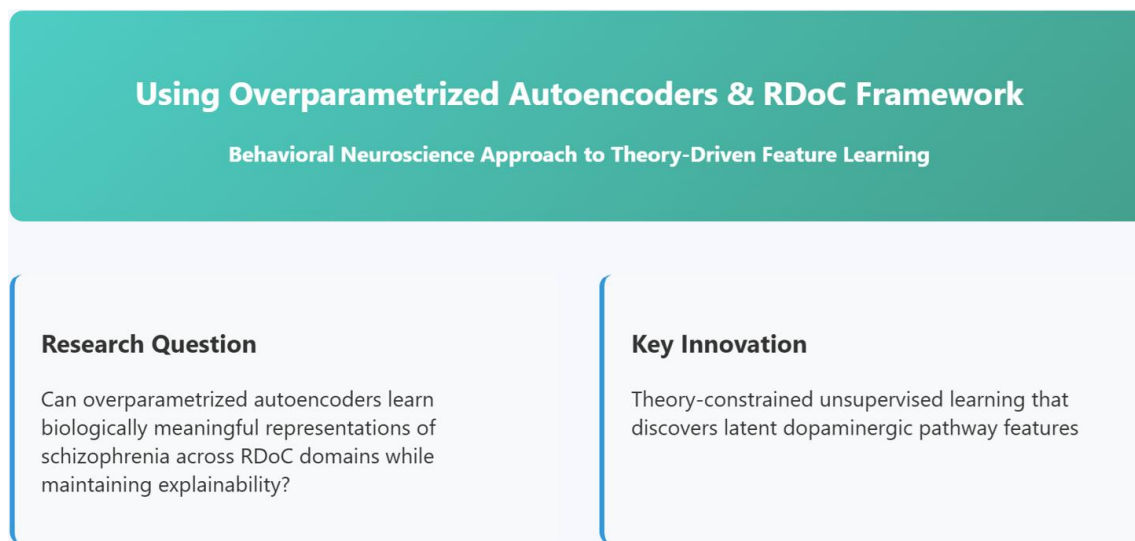
the Multi-Layer Perceptron Neural Networks (MLPNNs) discussed earlier—to demonstrate the versatility and adaptability of neurocomputational architectures in addressing diverse research questions within behavioral neuroscience applications as applied to behavioral phenotypes.

This comprehensive digital twin framework integrates SHAP explainability with overparameterized autoencoders, multimodal data fusion across RDoC levels of analysis, and robust regulatory compliance protocols (Cuthbert & Insel, 2013; Lundberg & Lee, 2017). The system leverages the empirically validated Framework B components (NPE, GNG_CE, SST_OE; partial $\eta^2 = .040$) as foundational features while incorporating Framework A's superior discriminative capacity (five features; partial $\eta^2 = .046$) for enhanced performance applications where computational efficiency is less critical. The research proposal is intended to stand alone and provide sufficient technical detail and implementation guidance to enable future researchers to develop and deploy clinically viable schizophrenia digital twin systems that meet FDA Software as Medical Device requirements while advancing precision computational psychiatry applications (FDA, 2021; Insel, 2014). It is listed below in a step-wise proposal fashion with figures to summarize the steps.

Research Framework and Methodological Innovation for Schizophrenia Digital Twins.

Figure 94

Explainable AI Digital Twin Development for Schizophrenia

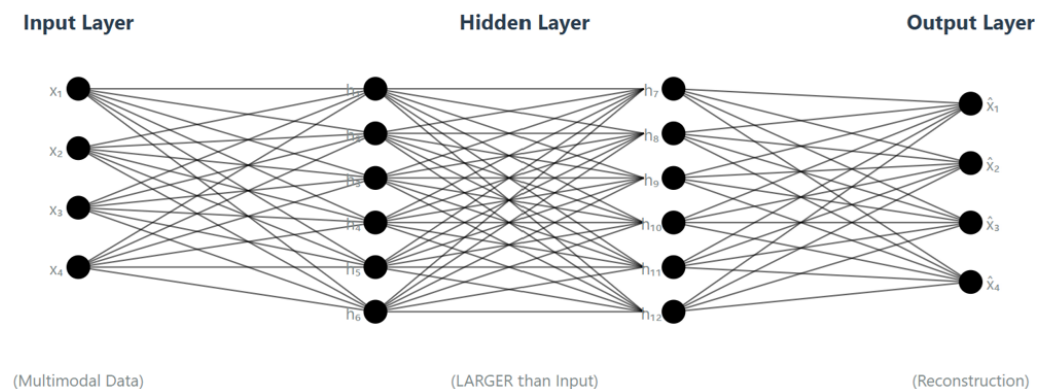
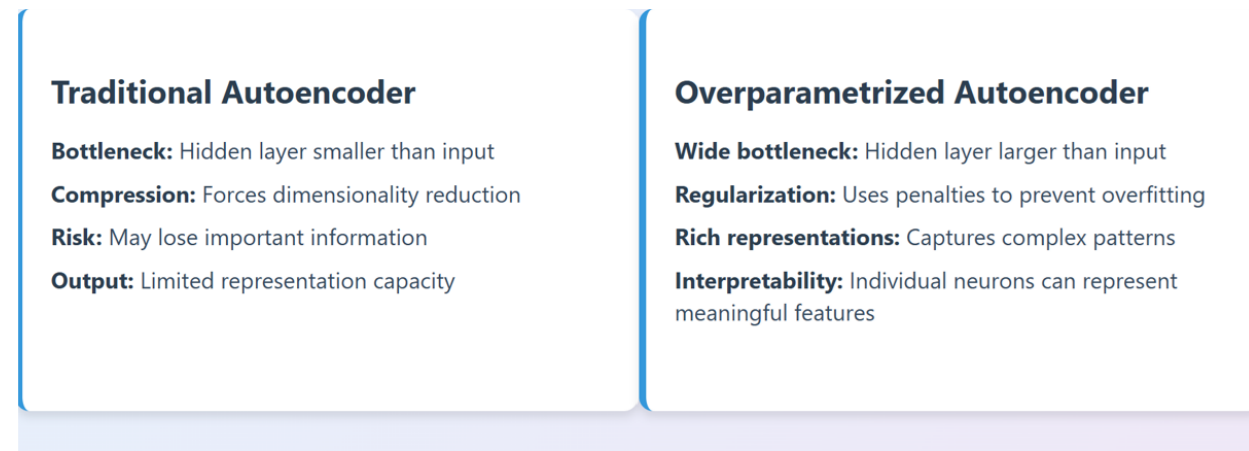


The proposed schizophrenia digital twin represents a potential advancement in explainable AI applications for computational psychiatry, combining overparameterized autoencoder (OAE) architectures with comprehensive SHAP explainability frameworks and RDoC-informed multimodal data integration (Bzdok & Meyer-Lindenberg, 2018; Insel et al., 2010). The research question driving this comprehensive approach asks: Can overparameterized autoencoders learn biologically meaningful representations of schizophrenia across RDoC domains while maintaining clinical explainability through SHAP value decomposition? The key innovation lies in theory-constrained unsupervised learning that discovers latent dopaminergic pathway features while providing transparent explanations for clinical decision support (Durstewitz et al., 2019; Grace, 2016).

Theoretical Foundation: From Traditional to Overparameterized Architectures.

Figure 95

Traditional Autoencoder versus Overparametrized Autoencoder



Overparametrized autoencoders consume considerably more computing resources than traditional autoencoders so it is important to support the logic of implementing an OAE over an AE in behavioral phenotype digital twin research. As described previously in this chapter, traditional autoencoder architectures employ bottleneck compression strategies that force dimensionality reduction, potentially losing critical pathway information essential for understanding schizophrenia's complex pathophysiology involving multiple neurotransmitter

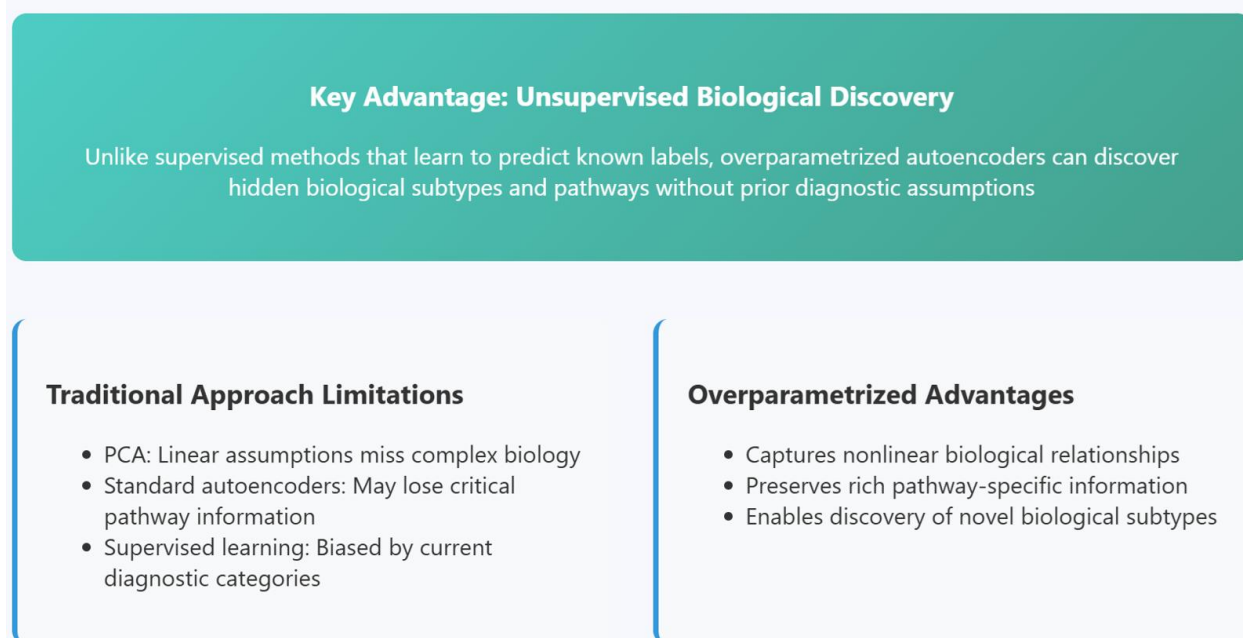
systems (e.g., dopamine, glutamate, GABA; Hinton & Salakhutdinov, 2006; Howes & Kapur, 2009).

Figure 96

Why Overparametrized Autoencoders for Schizophrenia



Overparameterized autoencoders address these limitations through wide bottleneck architectures that preserve rich representational capacity while employing regularization (penalty) techniques to prevent overfitting (Arpit et al., 2017; Zhang et al., 2021). This approach proves particularly suitable for schizophrenia's complex presentations involving positive symptoms (dopaminergic hyperactivity in mesolimbic pathways), negative symptoms (hypofunction in mesocortical dopamine combined with NMDA receptor hypofunction), and cognitive symptoms (gamma oscillation deficits with parvalbumin interneuron dysfunction; Grace, 2016; Lewis et al., 2005).

Figure 97*Advantages of Overparameterized Autoencoders for Schizophrenia Digital Twin Models*

The key advantage of the counterintuitive overparameterized autoencoder approach lies in unsupervised biological discovery. Unlike supervised methods that learn to predict known labels, overparameterized autoencoders can discover hidden biological subtypes and pathways without prior diagnostic assumptions (Arpit et al., 2017). Traditional approaches face significant limitations: PCA employs linear assumptions that miss complex biology, standard autoencoders may lose critical pathway information, and supervised learning remains biased by current nosologically diagnostic DSM categories (Hinton & Salakhutdinov, 2006). Overparameterized autoencoder advantages include capturing nonlinear biological relationships, preserving rich pathway-specific information, and enabling discovery of novel biological subtypes (Zhang et al., 2021).

The mathematical foundation extends the autoencoder framework described earlier for ASD applications, but with expanded latent dimensionality optimized for schizophrenia's multifactorial presentations (Goodfellow et al., 2016). For Framework B features $\mathbf{x} \in \mathbb{R}^3$, the encoder transformation becomes:

$$\mathbf{z} = f(\mathbf{x}) = \sigma(\mathbf{W}^e \mathbf{x} + b^e) \quad (100)$$

where $\mathbf{z} \in \mathbb{R}^d$ represents the overparameterized latent space with $d = 40-60$ dimensions for the three-dimensional Framework B input, $\mathbf{W}^e$ is the encoder weight matrix, b^e is the encoder bias vector, and σ is the activation function, providing expansion ratios of approximately 15-20:1 (Charte et al., 2018). The decoder reconstruction takes the form of

$$\hat{\mathbf{x}} = g(\mathbf{z}) = \sigma(\mathbf{W}^d \mathbf{z} + b^d) \quad (101)$$

where $\hat{\mathbf{x}}$ represents the reconstructed Framework B features, $g(\mathbf{z})$ is the decoder function, $\mathbf{W}^d$ is the decoder weight matrix, and b^d is the decoder bias vector that transforms the latent representation $\mathbf{z}$ back to the original three-dimensional feature space.

The loss function incorporates biological pathway constraints specific to schizophrenia pathophysiology (Tibshirani, 1996; Zou & Hastie, 2005):

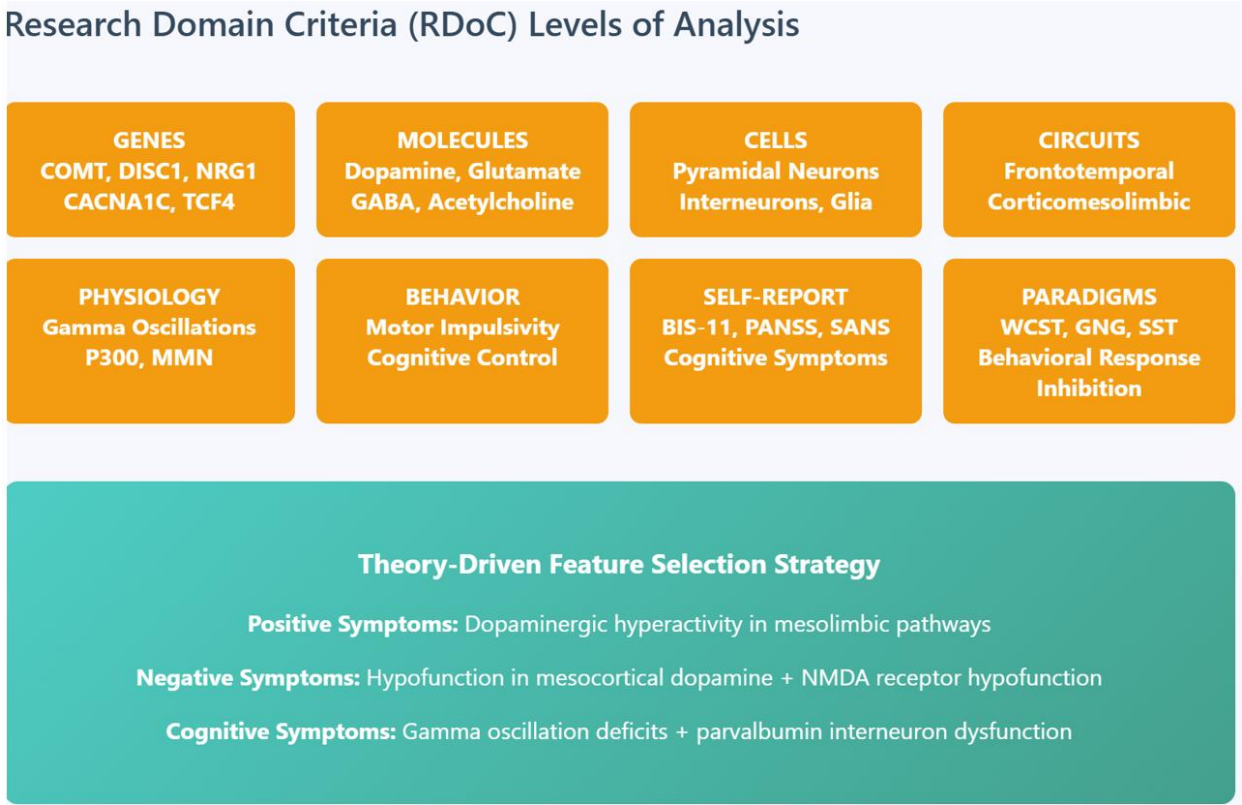
$$L = L_{recons} + \lambda_{pathway} \Omega_{pathway}(\mathbf{W}) + \lambda_{sparsity} \Omega_{sparsity}(\mathbf{z}) \quad (102)$$

where $\Omega_{pathway}(\mathbf{W})$ represents pathway-specific regularization encouraging biologically meaningful neuron clustering, and $\Omega_{sparsity}(\mathbf{z})$ promotes sparse activation patterns consistent with dopaminergic pathway dysfunction patterns observed in schizophrenia Grace, 2016; Howes et al., 2017).

RDoC Framework Application & Multimodal Integration for Schizophrenia Digital Twins.

Figure 98

RDoC Framework Applied to Schizophrenia Digital Twin



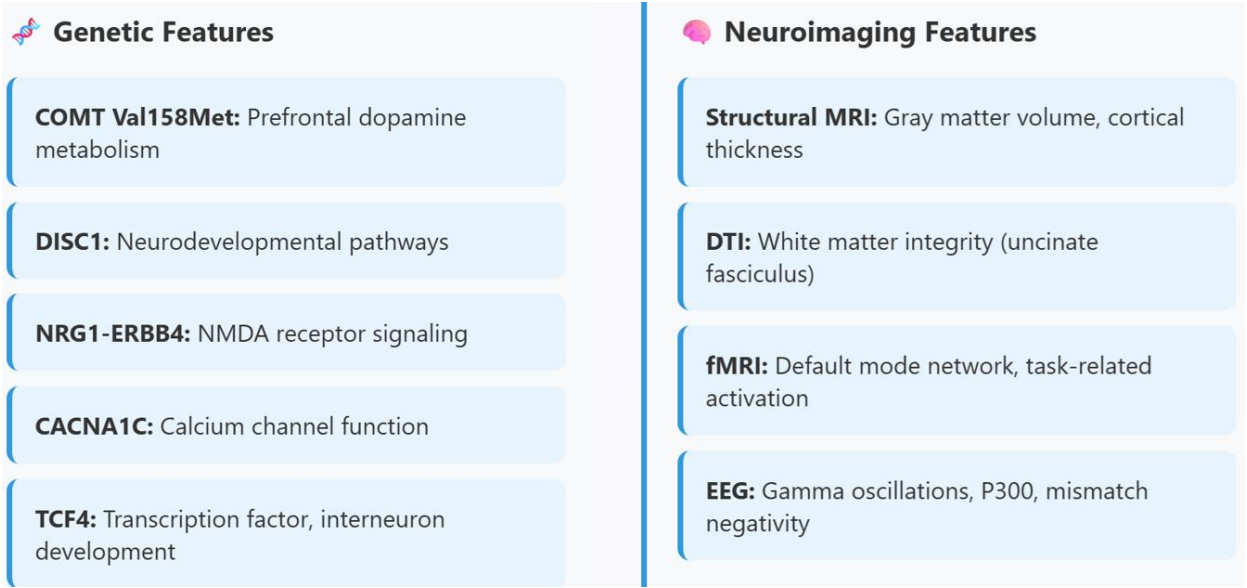
The schizophrenia digital twin architecture implements comprehensive RDoC-informed data integration across multiple levels of analysis, extending beyond Framework B behavioral measures to incorporate genetic, neuroimaging, cognitive, and clinical assessment modalities (Cuthbert & Insel, 2013; Morris & Cuthbert, 2012). As described in Chapter 2 and adapted to Schizophrenia, the Research Domain Criteria (RDoC) levels of analysis include: genes (COMT, DISC1, NRG1, CACNA1C, TCF4; Harrison & Weinberger, 2005; Owen et al., 2016), molecules

(dopamine, glutamate, GABA, acetylcholine; Grace, 2016; Howes & Kapur, 2009), cells (pyramidal neurons, interneurons, glia; Lewis et al., 2005), circuits (frontotemporal, corticomesolimbic Grace, 2016), neurophysiology (gamma oscillations, P300, MMN; Uhlhaas & Singer, 2010), behavior (motor impulsivity, cognitive control; Gold et al., 2009), self-report (BIS-11, PANSS, SANS, cognitive symptoms; Kay et al., 1987; Patton et al., 1995), and paradigms (WCST, GNG, SST, behavioral response inhibition [BRI]; Cuthbert & Insel, 2013; Gold et al., 2009; Nuechterlein et al., 2004).

The theory-driven feature selection strategy aligns with known schizophrenia pathophysiology: positive symptoms that reflect dopaminergic hyperactivity in mesolimbic pathways, negative symptoms that involve hypofunction in mesocortical dopamine combined with NMDA receptor hypofunction, and cognitive symptoms that result from gamma oscillation deficits with parvalbumin interneuron dysfunction (Grace, 2016; Lewis et al., 2005).

Figure 99

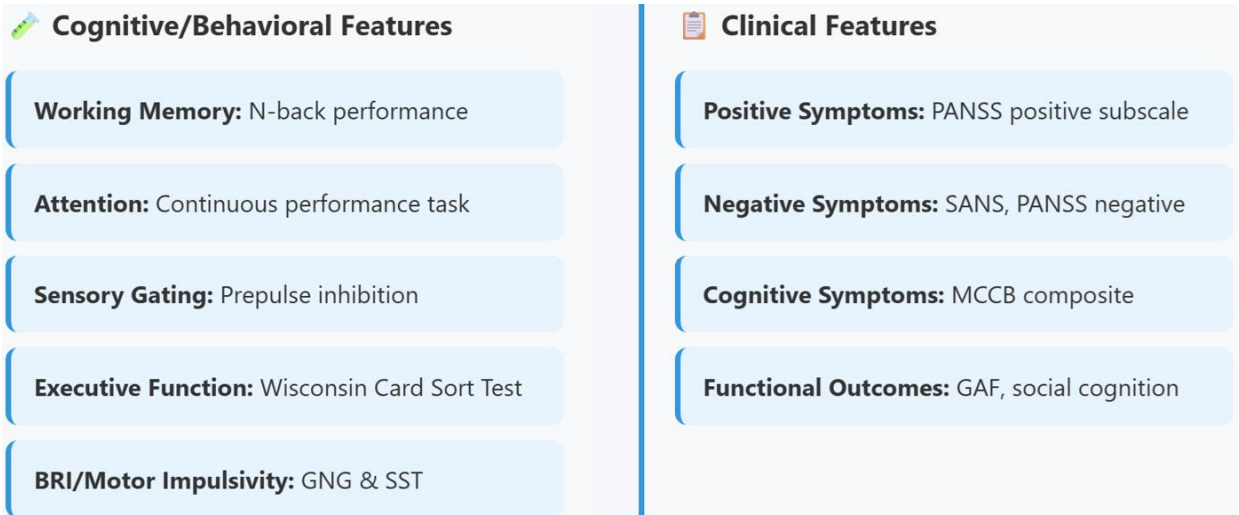
Multimodal Data Integration for Schizophrenia (Neurobiological & Neurophysiological)



As discussed in Chapter 2, genetic features of schizophrenia include key candidate polymorphisms: COMT Val158Met (prefrontal dopamine metabolism), DISC1 (neurodevelopmental pathways), NRG1-ERBB4 (NMDA receptor signaling), CACNA1C (calcium channel function), and TCF4 (transcription factor controlling interneuron development; Harrison & Weinberger, 2005; Owen et al., 2016). Neuroimaging features of schizophrenia encompass structural MRI (gray matter volume, cortical thickness), DTI (white matter integrity, particularly uncinate fasciculus), fMRI (default mode network connectivity, task-related activation patterns), and EEG (gamma oscillations, P300, mismatch negativity responses; Shenton et al., 2001; Uhlhaas & Singer, 2010).

Figure 100

Multimodal Data Integration for Schizophrenia (Cognitive & Clinical)



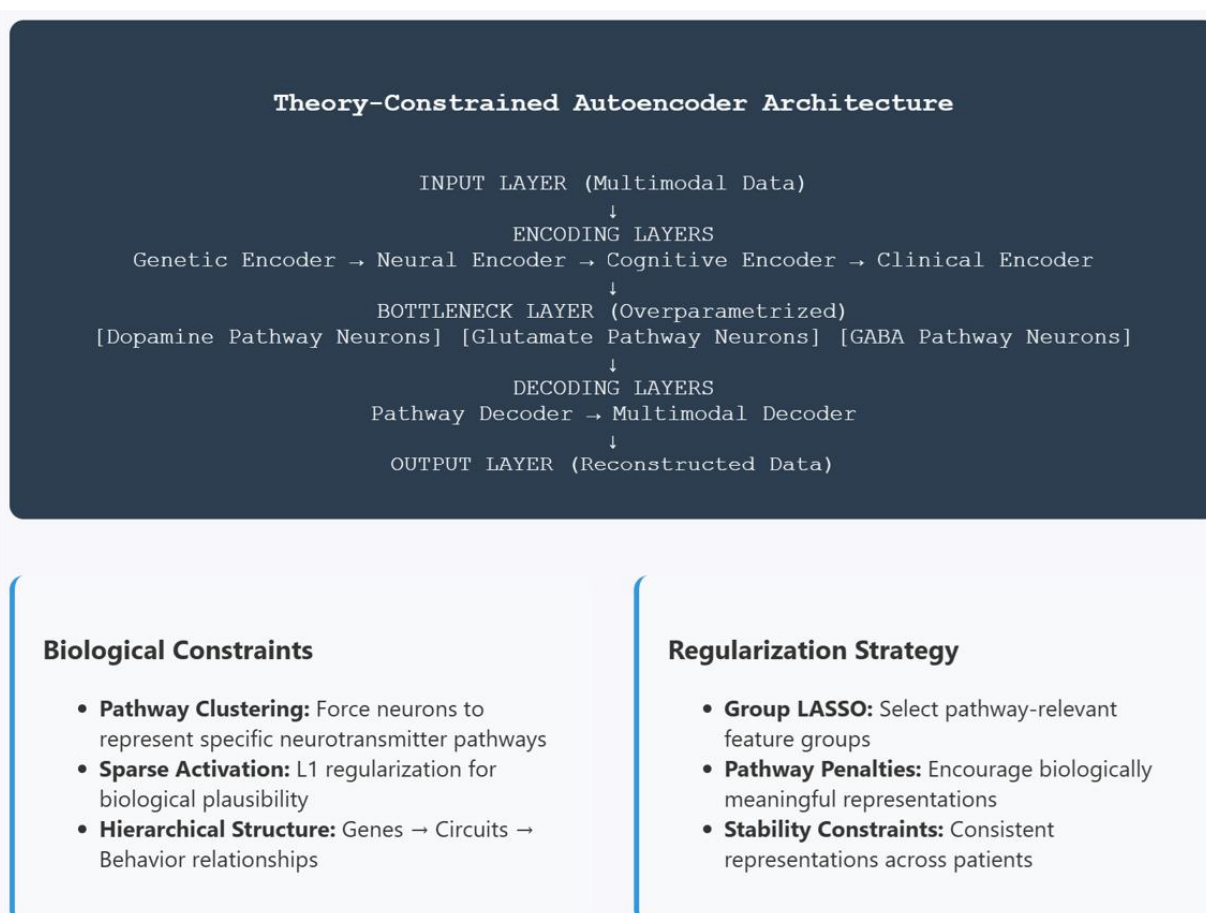
Cognitive and behavioral features of schizophrenia extend Framework B components through comprehensive assessment including working memory (N-back performance), attention (continuous performance task), sensory gating (prepulse inhibition), executive function

(Wisconsin Card Sorting Test [WCST]), and behavioral response inhibition (Go/No-Go [GNG] and Stop Signal Task [SST] measurements; Gold et al., 2009; Nuechterlein et al., 2004). Clinical features of schizophrenia incorporate positive symptoms (PANSS positive subscale), negative symptoms (SANS, PANSS negative), cognitive symptoms (MCCB composite), and functional outcomes (GAF under DSM IV-TR, social cognition assessments; Kay et al., 1987; Nuechterlein et al., 2008).

Theory-Constrained Architecture Design of OAE for Schizophrenia Digital Twins.

Figure 101

Schizophrenia Overparameterized Autoencoder Architecture



The overparameterized autoencoder (OAE) architecture for a schizophrenia digital twin implements biological constraints through pathway-specific neuron clustering in the bottleneck layer (Durstewitz et al., 2019). The architecture shown in Figure 101 follows a hierarchical structure implementing the RDoC matrix organization (Cuthbert & Insel, 2013):

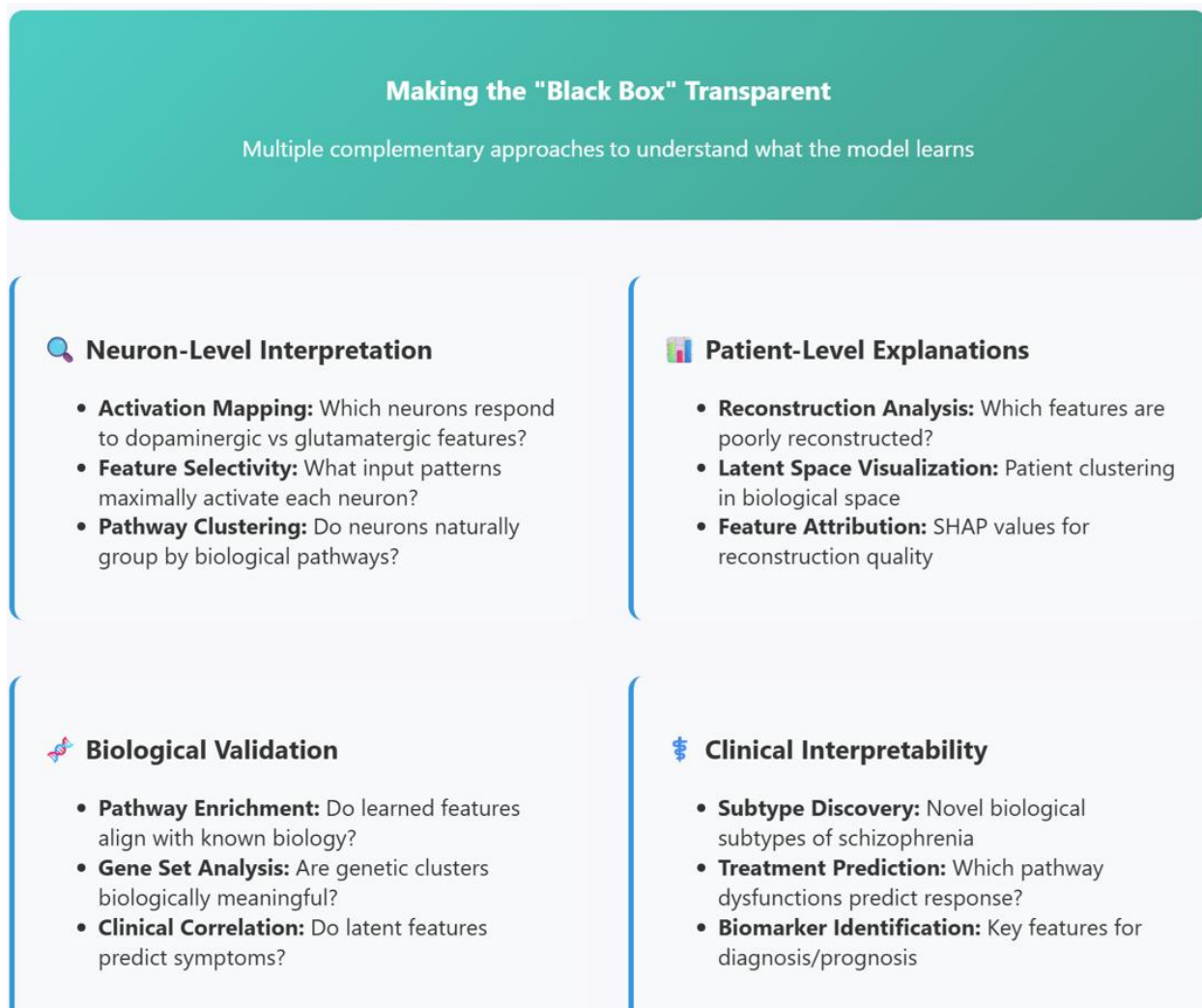
Biological constraints include pathway clustering (forcing neurons to represent specific neurotransmitter pathways), sparse activation (L1 regularization for biological plausibility), and hierarchical structure (preserving genes $\rightarrow$ circuits $\rightarrow$ behavior relationships; Grace, 2016; Lewis et al., 2005). The regularization strategy employs Group LASSO (see Chapter 2) for pathway-relevant feature group selection (Yuan & Lin, 2006), pathway penalties encouraging biologically meaningful representations, and stability constraints ensuring consistent representations across patients (Tibshirani, 1996).

Explainability Framework Implementation of OAE for Schizophrenia Digital

Twins.

Figure 102

Explainability in Overparameterized Autoencoders



The multi-level interpretation approach used for the schizophrenia digital twin makes the *black box* transparent through complementary analytical methods (Adadi & Berrada, 2018; Gunning et al., 2019). Neuron-level interpretation includes activation mapping (identifying

which neurons respond to dopaminergic versus glutamatergic features), feature selectivity analysis (determining input patterns that maximally activate each neuron), and pathway clustering verification (confirming neurons naturally group by biological pathways). Patient-level explanations encompass reconstruction analysis (identifying poorly reconstructed features), latent space visualization (patient clustering in biological space), and SHAP-based feature attribution for reconstruction quality assessment (Lundberg & Lee, 2017).

Biological validation protocols include pathway enrichment analysis (confirming learned features align with known biological pathways), gene set enrichment analysis (verifying genetic clusters are biologically meaningful), and clinical correlation studies (ensuring latent features predict symptom patterns; Subramanian et al., 2005). Clinical interpretability applications enable subtype discovery (identifying novel biological subtypes), treatment prediction (determining which pathway dysfunctions predict treatment response), and biomarker identification (discovering key features for diagnosis and prognosis; Kapur et al., 2012).

Comparative Analysis and Methodological Advantages of OAEs.

Figure 103

Overparameterized Autoencoders versus Traditional Approaches

Aspect	Traditional PCA/ICA	Standard Autoencoder	Overparametrized Autoencoder
Representation Capacity	Linear combinations only	Limited by bottleneck	Rich, nonlinear representations
Biological Constraints	None - purely statistical	Difficult to incorporate	Built into architecture
Multimodal Integration	Requires preprocessing	Basic concatenation	Sophisticated fusion mechanisms
Interpretability	Component loadings	Limited - compressed space	Individual neuron analysis
Novel Discovery	Limited to linear patterns	May miss complex interactions	Can discover hidden subtypes
Clinical Applicability	Research tool mainly	Difficult to explain	Clinically interpretable

Key Advantage: Biological Plausibility + Representational Power

Overparametrized autoencoders can capture the complex, nonlinear biology of schizophrenia while maintaining interpretability through biological constraints

Comparison across traditional PCA/ICA, standard autoencoders, and overparameterized autoencoders reveals distinct advantages across multiple dimensions: representation capacity, biological constraints, multimodal integration, interpretability, novel discovery potential, and clinical applicability. The key advantage of overparameterized approaches lies in biological plausibility combined with representational power—they capture the complex, nonlinear biology

of schizophrenia while maintaining interpretability through biological constraints (Durstewitz et al., 2019; Zhang et al., 2021).

Four-Phase Implementation Strategy for Schizophrenia Digital Twins.

Figure 104

Schizophrenia Digital Twin Four-Phase Implementation Strategy



The systematic development approach progresses through carefully designed phases that build upon previous accomplishments while maintaining scientific rigor and clinical utility (Proctor et al., 2011).

Phase 1: Data Preparation involves theory-driven feature selection using RDoC-guided variable selection as exemplified by this study (Cuthbert & Insel, 2013), multimodal normalization preserving scale relationships across data types (Hastie et al., 2019), biological annotation mapping features to known pathways (Subramanian et al., 2005), and comprehensive quality control including missing data handling and outlier detection protocols (Little & Rubin, 2019).

Phase 2: Architecture Design encompasses bottleneck sizing (2-5x input dimensionality based on multimodal feature complexity), pathway constraint implementation through biological regularization terms (Yuan & Lin, 2006), loss function optimization combining reconstruction accuracy with pathway penalties (Tibshirani, 1996), and activation function selection (ReLU for sparsity promotion; Glorot et al., 2011).

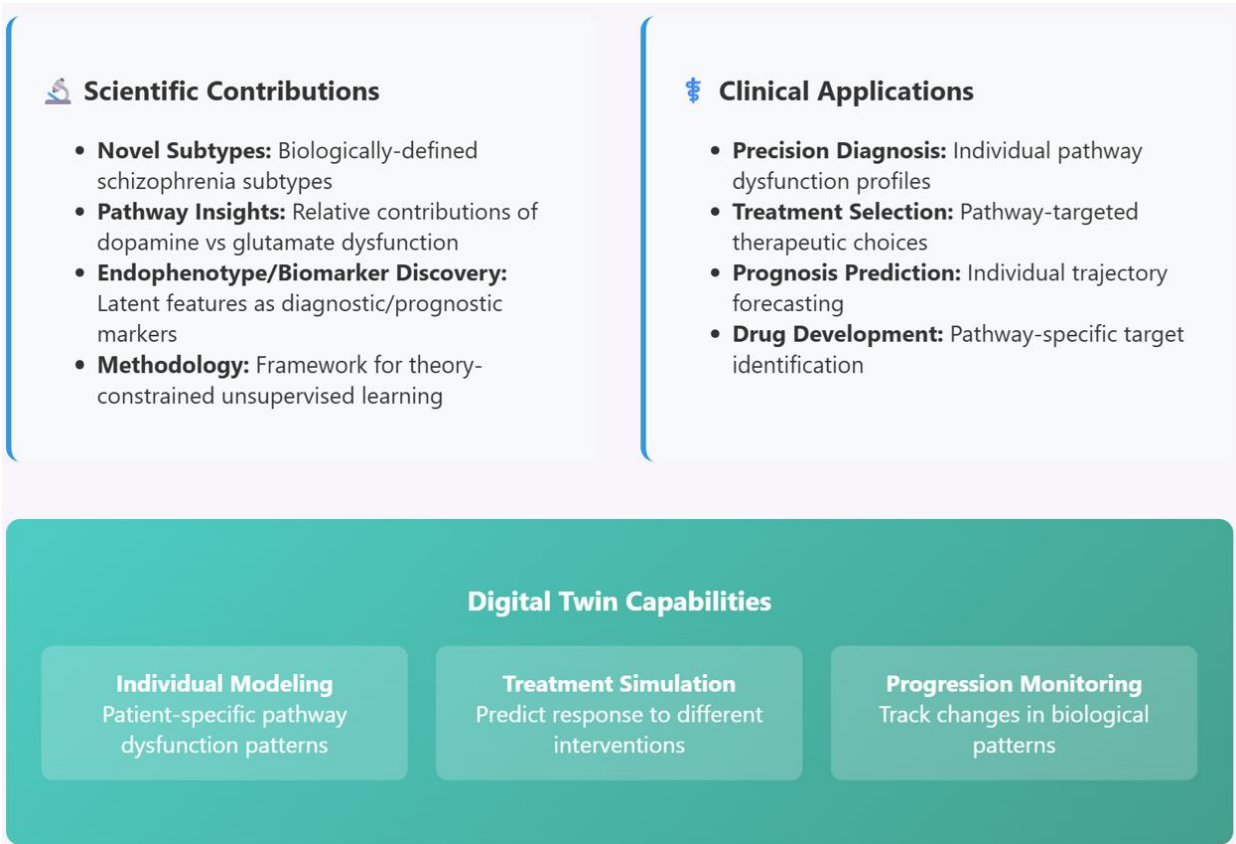
Phase 3: Training and Validation includes cross-validation stratified by clinical subtypes (Hastie et al., 2019), hyperparameter tuning optimizing regularization strength (Bergstra & Bengio, 2012), stability testing ensuring consistent representations (Boulesteix & Strobl, 2009), and convergence monitoring verifying biological constraint satisfaction throughout training (Goodfellow et al., 2016).

Phase 4: Interpretation and Validation incorporates neuron analysis revealing pathway-specific activation patterns, clinical validation measuring subtype prediction accuracy (Dwyer et al., 2018), biological validation through pathway enrichment analysis (Subramanian et al., 2005), and external validation using independent datasets to confirm generalizability (Steyerberg et al., 2001).

Expected Scientific and Clinical Outcomes for Schizophrenia Digital Twins.

Figure 105

Schizophrenia Digital Twin Expected Outcomes & Clinical Impact



The comprehensive schizophrenia digital twin modeling approach described here anticipates multiple categories of scientific contributions and clinical applications (Rasheed et al., 2020). Scientific contributions from the digital twin model include novel subtype discovery (biologically-defined schizophrenia subtypes transcending current diagnostic categories), pathway insights (quantifying relative contributions of dopamine versus glutamate dysfunction), endophenotype and biomarker discovery (identifying latent features serving as diagnostic and prognostic markers), and methodological advancement (establishing frameworks for theory-

constrained unsupervised learning in computational psychiatry; Durstewitz et al., 2019; Kapur et al., 2012).

Clinical applications encompass precision diagnosis through individual pathway dysfunction profiles (Insel, 2014), treatment selection optimization using pathway-targeted therapeutic choices (Kapur et al., 2012), prognosis prediction enabling individual trajectory forecasting (Koutsouleris et al., 2021), and drug development support through pathway-specific target identification (Krystal et al., 2017). Digital twin capabilities enable individual modeling (patient-specific pathway dysfunction patterns), treatment simulation (predicting responses to different interventions), and progression monitoring (tracking changes in biological patterns over time; Rasheed et al., 2020).

Regulatory Compliance and Clinical Translation Framework. The proposed schizophrenia digital twin system must integrate comprehensive regulatory compliance protocols from the initial development phases through clinical deployment and post-market surveillance (FDA, 2021). Documentation requirements include comprehensive AI/ML model development processes, training data characteristics, model architecture specifications, validation methodologies, and performance metrics across diverse populations, with specific emphasis on interpretability method validation and explanation accuracy assessment (FDA, 2024).

Explanation validation protocols must demonstrate that SHAP values, neuron activation patterns, and pathway clustering outputs accurately reflect genuine model decision processes rather than post-hoc rationalizations that could mislead clinicians. This requires systematic comparison of explanation consistency across different interpretability methods, evaluation of explanation stability across similar inputs, and validation that explanation-guided interventions produce expected clinical outcomes in schizophrenia populations.

Clinical Workflow Integration and Training Requirements. Successful deployment of the schizophrenia digital twin requires seamless integration with existing psychiatric assessment workflows while maintaining clinical standards and professional autonomy (Beam & Kohane, 2018; Topol, 2019). Framework B assessment protocols would be integrated into routine psychiatric evaluations, providing standardized deep endophenotype measurements that serve as validated inputs for the overparameterized autoencoder analysis.

Clinician training programs must develop competencies in interpreting ensemble predictions, evaluating SHAP-based feature attributions specific to schizophrenia pathophysiology, and recognizing situations where AI recommendations may be unreliable for complex psychotic presentations (Matheny et al., 2020; McCoy et al., 2020). Training would emphasize understanding of dopaminergic pathway interpretations, recognition of potential biases in genetic and neuroimaging feature weighting, and skills in communicating AI-derived diagnostic impressions to patients and families experiencing psychotic symptoms.

Post-Market Surveillance and Continuous Monitoring. The schizophrenia digital twin model system requires ongoing monitoring of diagnostic accuracy across demographic groups, particularly given documented disparities in schizophrenia diagnosis and treatment (Obermeyer et al., 2019). Automated monitoring systems would track prediction accuracy, pathway explanation consistency, user confidence in AI recommendations for psychotic presentations, and patient outcome improvements attributable to AI assistance in schizophrenia care.

Validation Metrics and Future Directions.

Figure 106

Schizophrenia Digital Twins Capabilities



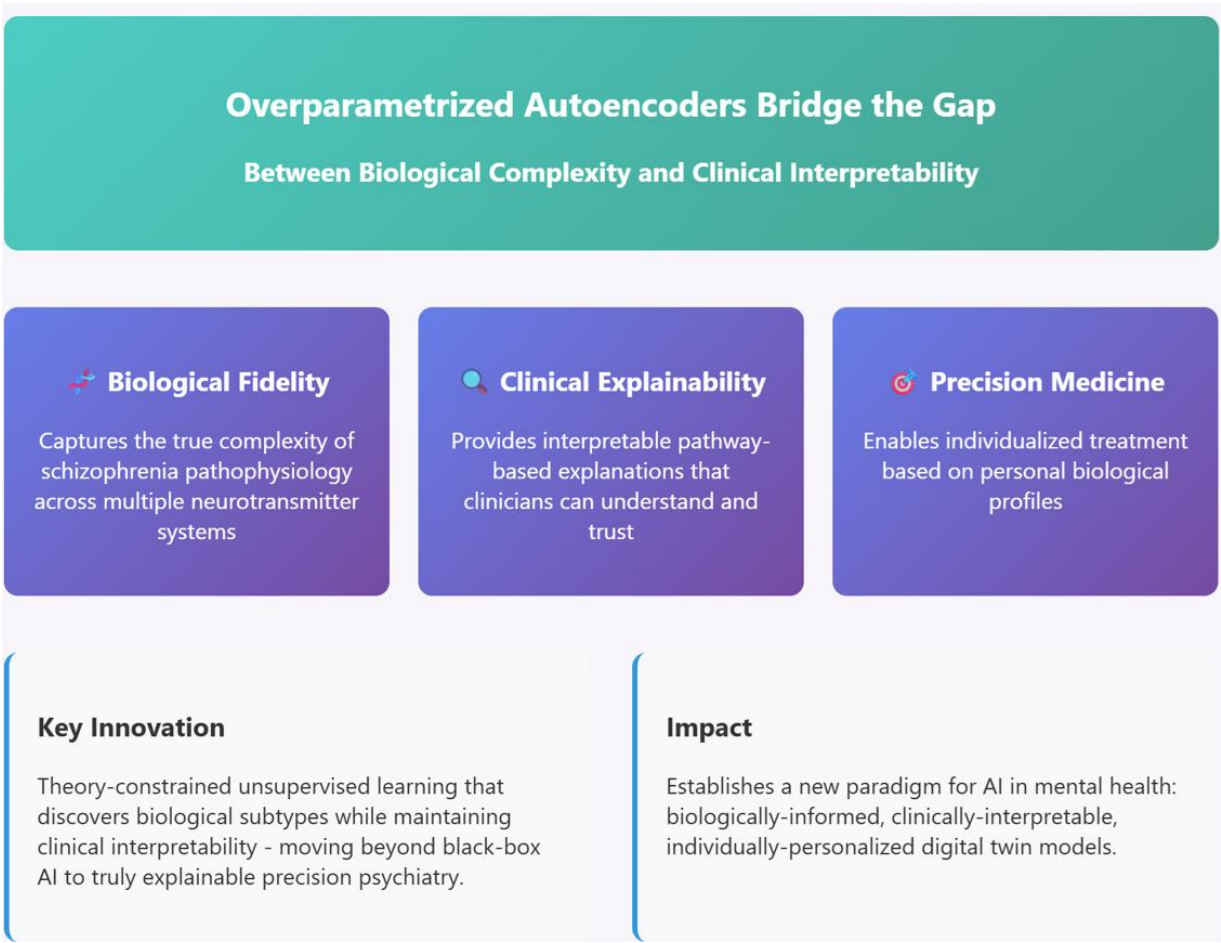
Comprehensive validation employs multiple complementary metrics including reconstruction quality (multimodal data fidelity), biological validity (pathway enrichment scores), clinical utility (symptom prediction accuracy), and stability (cross-validation consistency; Steyerberg et al., 2001). Digital twin capabilities encompass individual modeling (patient-specific pathway dysfunction patterns), treatment simulation (predicting responses to different interventions), and progression monitoring (tracking changes in biological patterns over time; Rasheed et al., 2020).

Additional future research directions include longitudinal modeling for disease progression tracking (Koutsouleris et al., 2021), treatment response prediction for medication effect forecasting (Krystal et al., 2017), multi-site validation ensuring generalizability (Dwyer et al., 2018), and real-time implementation supporting clinical decision-making (FDA, 2021).

Conclusion and Paradigm Advancement for Schizophrenia Digital Twins.

Figure 107

Conclusion: The Future of Explainable AI in Schizophrenia



The proposed overparameterized autoencoder digital twin modeling approach for schizophrenia discussed above bridges the gap between biological complexity and clinical

interpretability, providing biological fidelity that captures schizophrenia's true pathophysiological complexity across multiple neurotransmitter systems while maintaining clinical explainability through interpretable pathway-based explanations that clinicians can understand and trust (Durstewitz et al., 2019; Lundberg & Lee, 2017). The framework enables precision medicine through individualized treatment based on personal biological profiles, representing a key innovation in theory-constrained unsupervised learning that discovers biological subtypes while maintaining clinical interpretability—advancing beyond black-box AI toward truly explainable precision psychiatry (Insel, 2014; Topol, 2019).

The impact of the approach of this study of theoretic empirically validated deep decomposed endophenotypes as selected features for feature engineering for ensemble digital twins of behavioral phenotypes potentially establishes a new paradigm for AI in mental health: biologically-informed, clinically-interpretable, individually-personalized digital twin models that enhance rather than replace clinical expertise (Bzdok & Meyer-Lindenberg, 2018). This comprehensive framework demonstrates how careful integration of empirically validated endophenotype features, sophisticated AI architectures, rigorous explainability methods, and robust regulatory compliance can advance computational psychiatry toward clinically meaningful applications that improve patient outcomes while maintaining the transparency and accountability essential for healthcare practice.

Limitations and Future Directions

The current neurocomputational approaches for behavioral phenotype modeling, while promising, face several significant limitations that must be acknowledged and addressed through future research and development efforts (Bzdok & Meyer-Lindenberg, 2018; Durstewitz et al., 2019). These limitations span technical, clinical, and implementation domains, requiring

systematic investigation and innovation to realize the full potential of AI-assisted behavioral phenotype assessment in clinical practice (Rajkomar et al., 2018; Topol, 2019).

Current Technical Limitations. The Framework B endophenotype approach, while empirically validated in this study, represents a significant dimensionality reduction from the complex, multifaceted nature of behavioral phenotypes that may not capture important aspects of presentation variability, a specific concern with the literature and AI modeling approaches discussed in Chapter 2 (Cuthbert & Insel, 2013; Lilienfeld, 2014). The three-component structure, while mathematically tractable and clinically interpretable, may oversimplify the rich behavioral patterns that characterize ADHD, ASD, schizophrenia, and BPD presentations in real-world clinical populations (Borsboom et al., 2011; Kapur et al., 2012). Frameworks A, C, and D can provide additional or alternative complexity. However, as discussed in Chapter 2, the endophenotype decomposition approach can provide additional, richer, more discriminating features for neurocomputational AI models. The decomposition and recomposition process that led to Framework B provides empirically validated feature engineering and a similar approach can be implemented across RDoC's multi-modal domains and units of measure. The comprehensive schizophrenia digital twin approach addresses some of these limitations through multimodal RDoC integration and overparameterized architectures that preserve pathway-specific information, but computational resource requirements and technical complexity remain significant barriers to widespread clinical adoption.

Ensemble digital twin architectures require substantial computational resources and technical expertise that may limit accessibility for smaller clinical practices or resource-constrained healthcare systems (Chen & Asch, 2017; Rajkomar et al., 2019). The mathematical complexity of Bayesian model averaging, meta-learning optimization, and uncertainty

propagation through ensemble predictions necessitates specialized technical expertise, support, and infrastructure that may not be readily available in most clinical settings (Beam & Kohane, 2018; Ghahramani, 2015).

Explainable AI methods, while providing valuable insights into model decision-making processes, may not fully address the interpretability needs of all clinical stakeholders (Holzinger et al., 2017; Rudin, 2019). SHAP values and attention mechanisms provide mathematical explanations that require technical understanding to interpret appropriately, potentially creating barriers for clinicians without extensive statistical or machine learning backgrounds (Molnar, 2020; Ribeiro et al., 2016).

Clinical Validation Challenges. The transition from controlled research settings to real-world clinical practice introduces numerous confounding variables and implementation challenges that may affect system performance and clinical utility (Glasgow et al., 2003; Singal et al., 2014). Clinical populations exhibit greater heterogeneity, comorbidity complexity, and presentation variability than research samples, potentially reducing the generalizability of model predictions and explanations developed on research datasets (Kennedy-Martin et al., 2015; Rothwell, 2005).

As with healthcare solutions generally, longitudinal validation of AI-assisted diagnostic decisions requires extended follow-up periods and comprehensive outcome tracking that may be difficult to implement in routine clinical practice (Black, 1996; Concato et al., 2000). The gold standard for behavioral phenotype diagnosis remains clinical consensus based on comprehensive evaluation, creating circular validation challenges where AI systems are evaluated against potentially imperfect human judgment standards (Frances, 2013; Spitzer, 1983).

Cultural and demographic diversity in clinical populations may reveal biases or limitations in AI models trained on research samples that lack adequate representation of minority populations, non-English speakers, or individuals from different socioeconomic backgrounds (Chen et al., 2019; Obermeyer et al., 2019). Ensuring equitable performance across diverse populations would require ongoing validation studies and potential model retraining with more representative datasets (Larrazabal et al., 2020; Rajkomar et al., 2018). The proposed schizophrenia digital twins face additional validation challenges specific to psychotic disorders, including the episodic nature of symptoms, medication effects on cognitive performance, and the difficulty of obtaining comprehensive multimodal data during acute psychiatric episodes. Cultural factors affecting symptom expression and help-seeking behavior in psychotic disorders require particular attention in model validation across diverse populations.

Future Research Priorities. Multimodal RDoC integration represents a critical area for future development, incorporating neuroimaging, genetic, physiological, neurobiological, neuropsychological, and environmental data alongside Framework B deep endophenotypes to create more comprehensive behavioral phenotype models (Cuthbert & Insel, 2013; Insel et al., 2010). Advanced fusion architectures could leverage complementary information sources while maintaining interpretability and clinical utility essential for practical implementation (Baltrusaitis et al., 2019; Lahat et al., 2015).

Causal modeling approaches offer promising directions for understanding mechanistic relationships between endophenotype deficits and behavioral presentations, enabling more targeted interventions and improved treatment response prediction (Hernán & Robins, 2020; Pearl & Mackenzie, 2018). Causal AI methods could reveal intervention targets and treatment

mechanisms that optimize therapeutic outcomes while minimizing adverse effects (Peters et al., 2017; Spirtes et al., 2000).

Federated learning frameworks represent essential developments for enabling multi-site collaboration while preserving patient privacy and data security (Li et al., 2020; McMahan et al., 2017). Large-scale federated studies could generate more robust and generalizable models while addressing rare behavioral phenotype combinations and cultural diversity considerations that require substantial sample sizes (Kaissis et al., 2020; Rieke et al., 2020).

Adaptive learning systems that continue improving through clinical deployment could address model drift, population changes, and evolving clinical practices that affect long-term system performance (Chen et al., 2018; Lu et al., 2018). However, adaptive systems require sophisticated change control protocols and regulatory frameworks that balance improvement opportunities with safety and validation requirements (FDA, 2021; Heaven, 2019).

Personalized AI approaches that adapt model architectures and predictions based on individual characteristics could improve accuracy and clinical utility for specific patient populations (Ashley, 2016; Hamburg & Collins, 2010). Further, precision medicine applications could optimize intervention selection and psychopharmacological dosing based on predicted treatment responsiveness derived from comprehensive behavioral phenotype, endophenotype, and biomarker profiles (Collins & Varmus, 2015; Ginsburg & Phillips, 2018). The development of standardized evaluation frameworks for clinical AI systems represents another critical priority, enabling systematic comparison of different approaches and establishment of performance benchmarks for regulatory approval and clinical adoption (Liu et al., 2019; Vasey et al., 2021). Standardized metrics and validation protocols could accelerate innovation while ensuring safety

and effectiveness standards across different AI implementations (Park et al., 2020; Sendak et al., 2020).

Conclusion

This study successfully resolved the fundamental problem described in Chapters 1 and 2, that “the endophenotype literature does not adequately characterize and segregate the dimensionality of the latent psychological constructs of impulsivity and impulse control” by demonstrating that behavioral response inhibition (BRI) can be decomposed into robust, measurable facets that reliably discriminate trait motor impulsivity groups. Through systematic MANOVA analysis enhanced by Cook's distance leverage-residual sensitivity analysis across 480 participants, the study identified Framework B (Model Representative; NPE + GNG_CE + SST_OE) as achieving the most optimal power-parsimony balance, partial $\eta^2 = .040$, $p < .001$, and Framework A (Optimal Performance; NPE, GNG_CE, GNG_OE, SST_OE, SSRT) five deep endophenotype feature set providing the largest effect size combination, partial $\eta^2 = .046$, among multiple statistically significant endophenotype combinations, providing empirically-validated deep decomposed endophenotypes for neurocomputational AI applications in behavioral phenotype modeling.

Central Research Discovery

The central discovery of this study is that endophenotype decomposition combined with methodological precision can resolve longstanding trait-state measurement discordance while revealing genuine behavioral control (BRI) mechanisms that traditional approaches systematically underestimate. The successful identification of Framework B components as influence-resistant, neurobiologically-grounded markers (deep endophenotypes) demonstrates that complex psychological constructs are not inherently unmeasurable, but rather require

sophisticated analytical approaches that preserve latent discriminative information rather than collapsing it through premature dimensional reduction. This finding arguably fundamentally transforms behavioral response inhibition from a problematic unitary construct into a systematic framework of empirically validated candidate endophenotypes with clear pathways for validation and advanced neurocomputational modeling applications.

Theoretical and Clinical Significance

The findings of this study represent a paradigm shift from previous research that struggled with weak correlations between trait and state impulsivity measures (e.g., Aichert et al.'s 12% variance explained) to robust group discrimination through endophenotype decomposition. The study validated the RDoC framework's dimensional approach while providing the empirical foundation that has been missing for precision psychiatry applications. The reconceptualization of GNG and SST tasks as measuring impulsivity versus compulsivity control mechanisms, respectively, arguably resolves decades of measurement confusion and establishes clear predictions for neurobiological validation.

The discovery of differential speed-accuracy optimization patterns via a reaction time threshold—where high trait motor impulsivity individuals achieve optimal performance at 558ms versus 625ms reaction time thresholds—challenges fundamental assumptions underlying current interventions and provides neurobiological rationale for personalized treatment approaches. This finding has immediate clinical implications for ADHD, ASD, schizophrenia, and BPD populations, suggesting that interventions should capitalize on rather than override individual neural efficiency patterns.

The neurobiological plausibility of the reaction time threshold discovery gains support from its temporal convergence with established N2 ERP component timing, suggesting that

optimal behavioral performance emerges from efficient neural processing cascades spanning approximately 290-360 milliseconds from initial conflict detection to behavioral execution. This multi-level validation strengthens confidence in the clinical utility of reaction time threshold profiling for personalizing intervention approaches across behavioral phenotypes.

The successful discrimination between motor and choice impulsivity subtypes through WCST pattern analysis—preserved perseverative responses (PR) indicating intact caudate nucleus (CN) function alongside elevated non-perseverative errors (NPE) reflecting motor impulsivity-specific dysfunction—demonstrates the utility of phenolog-based approaches for advancing precision psychiatry applications across diverse behavioral phenotypes.

The identification of phenotypic heterogeneity within control groups—specifically the discovery of a choice impulsivity subgroup among low motor impulsivity individuals as reported in Chapter 4—demonstrates the sophisticated discriminative capacity of endophenotype decomposition approaches. This finding validates the utility of multidimensional assessment strategies for revealing hidden neurobiological complexity that traditional unitary approaches systematically miss, supporting the transition toward precision psychiatry applications based on individual endophenotype profiles rather than categorical diagnostic classifications.

Neurocomputational AI Applications and Digital Twin Innovation

The comprehensive neurocomputational applications framework developed in this chapter demonstrates how empirically validated endophenotypes can serve as the foundation (as selected and engineered features) for sophisticated AI-enabled clinical tools. The progression from individual model architectures optimized for specific behavioral phenotype characteristics through ensemble digital twin systems represents a systematic approach to leveraging AI capabilities while maintaining clinical interpretability and regulatory compliance.

The comprehensive schizophrenia digital twin exemplar illustrates how overparameterized autoencoders can capture complex pathophysiological processes across multiple neurotransmitter systems while providing transparent explanations through SHAP values and biological pathway clustering. The integration of RDoC-informed multimodal data with theory-constrained unsupervised learning creates opportunities for discovering novel biological subtypes and optimizing treatment selection based on individual pathway dysfunction profiles.

The explainable AI frameworks address critical regulatory requirements for medical device approval while ensuring that clinical decision support maintains the transparency and accountability essential for healthcare practice. The systematic integration of interpretability methods with comprehensive validation and monitoring frameworks provides a roadmap for responsible research, development, and deployment of AI systems in psychiatric care.

Research Program Foundation and Clinical Translation

The validated Framework B deep decomposed endophenotypes establish the measurement foundation necessary for the comprehensive research program outlined in this chapter, from immediate empirical extensions through sophisticated neurocomputational applications. The Generic Model Study framework provides systematic methodology for integrating genetic (neurobiological), neuroimaging (neurophysiological), neuropsychological, and clinical assessment modalities around these validated behavioral anchors, potentially reviving and advancing RDoC candidate gene research through improved measurement precision.

The clinical translation framework addresses implementation challenges through systematic attention to workflow integration, clinician training, and evidence generation

protocols. The progression from research prototypes to clinical deployment requires comprehensive consideration of organizational change management, human factors engineering, and performance monitoring systems that ensure real-world effectiveness and safety.

Field Transformation and Future Directions

This study fundamentally advances computational and behavioral neuroscience by demonstrating that reductionist endophenotype decomposition enables rather than opposes emergent systems modeling, providing the theoretical synthesis necessary for sophisticated applications in computational psychiatry. The successful integration of methodological innovation, theoretical reconceptualization, and technological application establishes a comprehensive framework for understanding complex neurobiological systems while providing practical tools for improving differential diagnosis and personalizing interventions.

The transformation from endophenotype characterization problems to validated measurement solutions, from trait-state discordance to robust discrimination, and from categorical diagnostic confusion to objective behavioral profiling demonstrates that sophisticated analytical approaches can resolve fundamental challenges that have limited progress in psychiatric research. The neurocomputational applications provide pathways for transitioning from symptom-based to mechanism-based approaches in behavioral neuroscience, computational psychiatry, and clinical practice.

Future research priorities include expanding multimodal RDoC integration, developing causal modeling approaches for understanding mechanistic relationships, implementing federated learning frameworks for multi-site collaboration, and creating adaptive learning systems that continue improving through clinical deployment. The establishment of standardized evaluation frameworks for clinical AI systems represents a critical priority for systematic

comparison of different approaches and establishment of performance benchmarks for regulatory approval and clinical adoption.

These advances provide the empirical foundation necessary for next-generation precision psychiatry applications that enhance rather than replace clinical expertise, advancing the field toward biologically-informed, clinically-interpretable, individually-personalized assessment and intervention approaches that improve patient outcomes while maintaining the transparency and accountability essential for healthcare practice.

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Appendix A

IRB Approval Letters



9388 Lightwave Ave.
San Diego, CA 92123
irb@nu.edu

Notice of Exemption

December 12, 2023

To: John Wehrli

Project Title: Neurobiological and Neuropsychological Endophenotypes of Behavioral Response Inhibition: RDoC Latent Variable Endophenotype Decomposition; Inputs for Neurocomputational AI Models of Four Behavioral Phenotypes

NU IRB Number: IRB-FY23-24-275

Determination: Exempt from further review 45 CFR 46.101 Category 2.(i). Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

Status: Active - Research activities may begin as of December 12, 2023

Dear John Wehrli:

The study referenced above has been reviewed by the National University IRB. The IRB has determined your research is exempt from further review under 45 CFR 46.104, which means you will not need to renew your study and may begin your study effective immediately. However, if you find the need to change your study in any way, you will need to submit a modification to the IRB prior to implementing the changes. This will allow the IRB to determine whether or not the study still meets exemption criteria.

Please review your Post Approval Responsibilities here: [Approved Documents Guidelines](#)

For any questions regarding your protocol, please reach out to the IRB at irb@nu.edu.

Sincerely,

A handwritten signature in cursive script, appearing to read 'Joseph M. Marron'.

Dr. Joseph Marron, IRB Chair

A handwritten signature in cursive script, appearing to read 'Brianne Mongeon'.

Dr. Brianne Mongeon, Director, HRPP & IRB

A handwritten signature in cursive script, appearing to read 'Jenessa Eberhardt'.

Jenessa Eberhardt, Associate Director, HRPP & IRB



9388 Lightwave Ave.
San Diego, CA 92123
irb@nu.edu

Notice of Exemption

June 5, 2024

To: John Wehrli

Project Title: Neurobiological and Neuropsychological Endophenotypes of Behavioral Response Inhibition: RDoC Latent Variable Endophenotype Decomposition; Inputs for Neurocomputational AI Models of Four Behavioral Phenotypes

NU IRB Number: IRB-FY23-24-275

Modification Determination: Exempt from further review 45 CFR 46.101

Status: Active - Research activities may begin as of June 5, 2024

Dear John Wehrli:

The study referenced above has been reviewed by the National University IRB. The IRB has determined the proposed modification to your research is exempt from further review under 45 CFR 46.101, which means you will not need to renew your study and may begin your study effective immediately. However, if you find the need to change your study in any way, you will need to submit a modification to the IRB prior to implementing the changes. This will allow the IRB to determine whether or not the study still meets exemption criteria.

Please review your Post Approval Responsibilities here: [Approved Documents Guidelines](#)

For any questions regarding your protocol, please reach out to the IRB at irb@nu.edu.

Sincerely,

A handwritten signature in cursive script, appearing to read 'Joseph M. Marron'.

Dr. Joseph Marron, IRB Chair

A handwritten signature in cursive script, appearing to read 'Brianne Mongeon'.

Dr. Brianne Mongeon, Director, HRPP & IRB

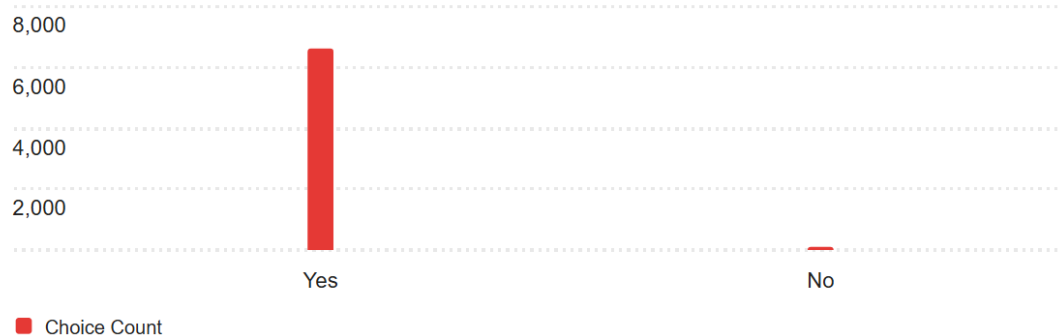
A handwritten signature in cursive script, appearing to read 'Jenessa Eberhardt'.

Jenessa Eberhardt, Associate Director, HRPP & IRB

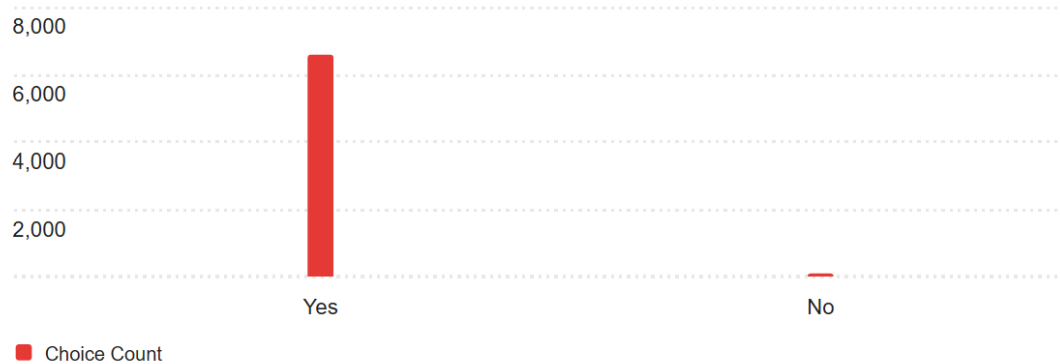
Appendix B

Qualtrics Survey

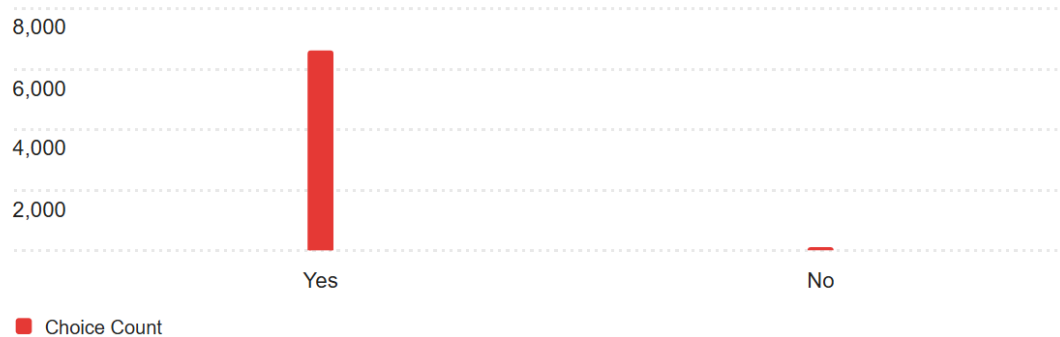
Q1 - Are you using a computer (Windows or Mac) with a keyboard to complete the study?



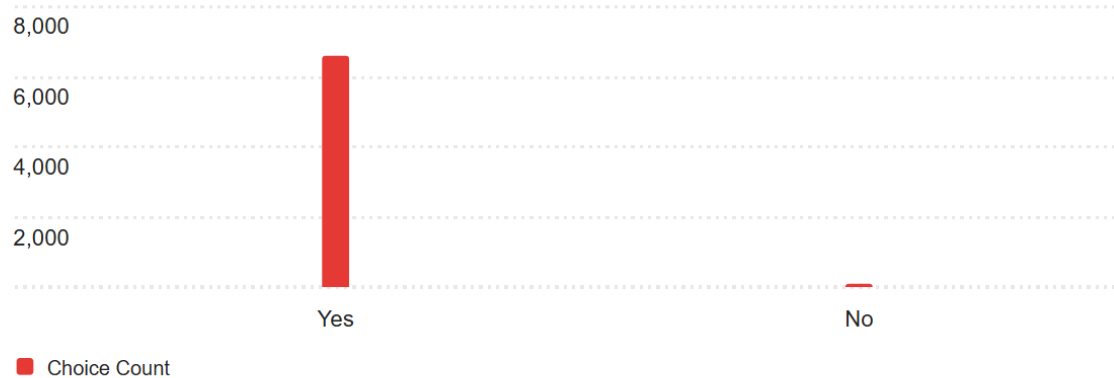
Q2 - Are you age 18-40?



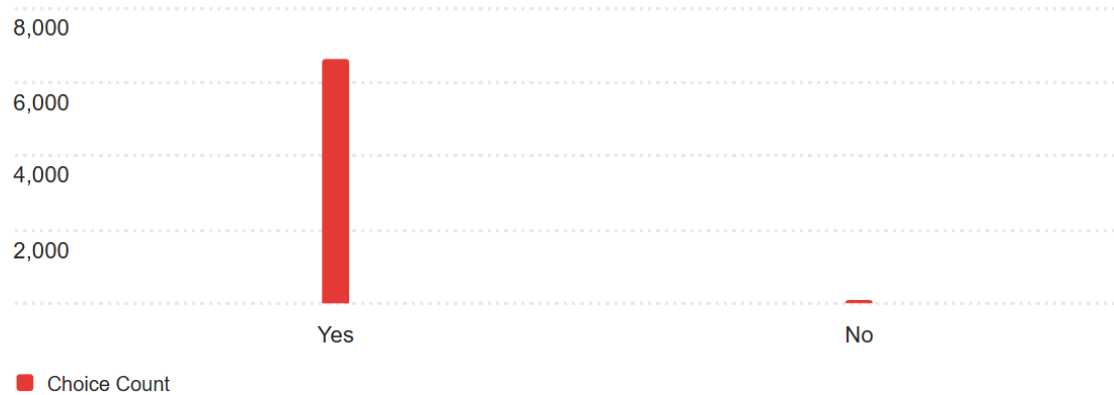
Q3 - Are you right-handed?



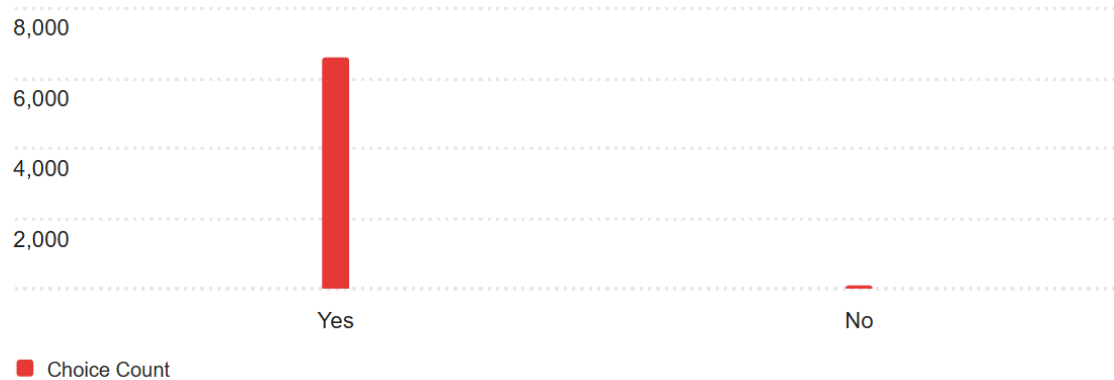
Q4 - Do you have normal hearing without a hearing aid?



Q5 - Do you have normal vision with (or without) corrective lenses?



Q6 - Do you see color normally (are you not color blind)?



Informed Consent

Qualtrics/NCU Online Anonymous Study/Questionnaire Informed Consent

Hello,

My name is John Wehrli, and I am a doctoral student at Northcentral University (part of National University). I am conducting an online survey to understand the association between various measures of impulsivity and how people differ on those measures.

In order to participate, you must be 18-40 years of age, right-handed, have normal hearing (unaided), and not color blind and be able to read English at least at the 7th grade level. If you were directed to this form, but do not meet the above criteria, please stop now and click **'Exit Study'** below.

The following survey and laboratory measures **MUST BE COMPLETED ON A PC OR MAC WITH A KEYBOARD (DO NOT USE A CELL PHONE OR IPAD OR A TOUCHSCREEN)** with minimal distraction and includes:

Demographic Questions:

- biological sex at birth **(required)**
- gender identity (optional)
- exact age (optional)
- race and ethnicity (optional)
- education level (optional)
- mental health diagnosis (optional)
- use of medications or drugs (optional)

Questions related to impulsivity **(required)**. 1-5 min.

Three separate interactive testing instruments that measure different aspects of impulsivity **(required)**

- one about 8-12 min.
- one about 10-15 min
- one about 3-6 min

It will take **30 to 45** minutes of your time to complete the entire survey (including all screening and demographic questions and testing instruments) in one sitting. Please plan on spending at least that amount of time without distraction.

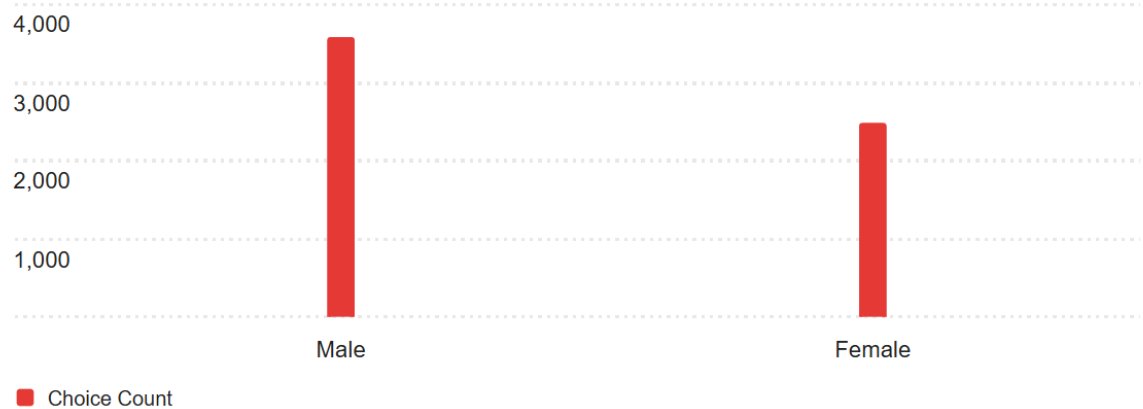
NOTE: In order to run the interactive testing instruments, you will be required to install a free Inquisit app from Millisecond Software onto your computer when prompted to do so by following the simple instructions. You can delete the app after you complete the study. **IF YOU DO NOT WANT TO INSTALL THE APP, PLEASE CLICK 'EXIT STUDY' BELOW.**

Your participation in this study is voluntary. If you decide to participate, **your responses will be anonymous** - that is, recorded without any identifying information that is linked to you. If you have any questions regarding this survey, please contact me at j.wehrli2110@o365.ncu.edu.

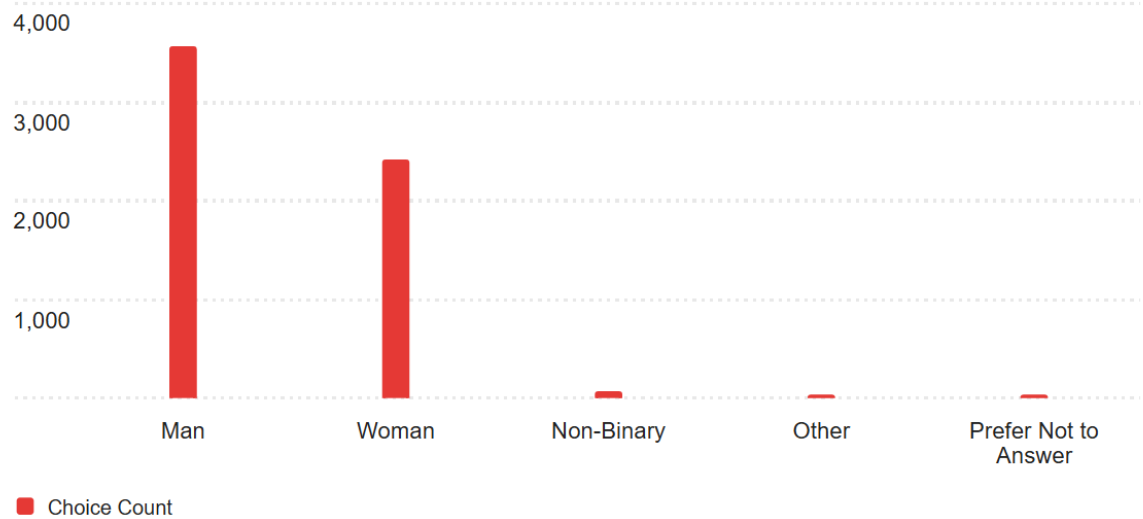
If you have any questions regarding your rights as a human subject and participant in this study, or to report research-related problems, you may email the National University IRB at irb@nu.edu.

By clicking the 'I Accept' button and completing the survey you certify that you meet the Acceptance Criteria and indicate that you have consented to participate in this research. If you do not want to participate, please press 'Exit Study' below.

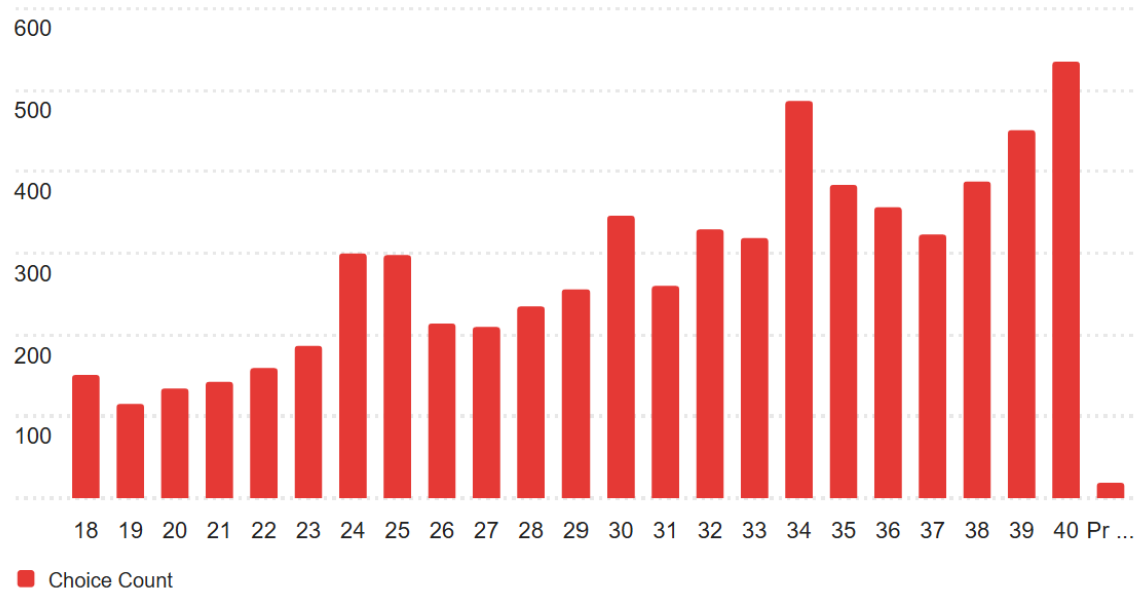
Q24 - Biological Sex at Birth



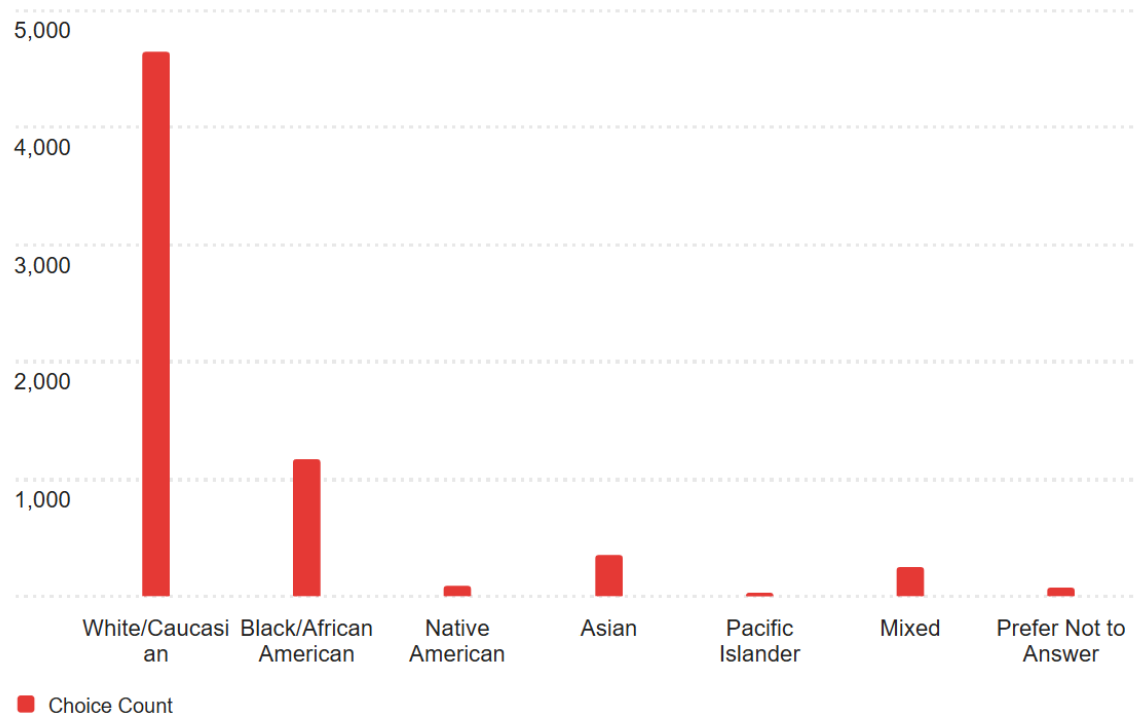
Q25 - Gender Identity



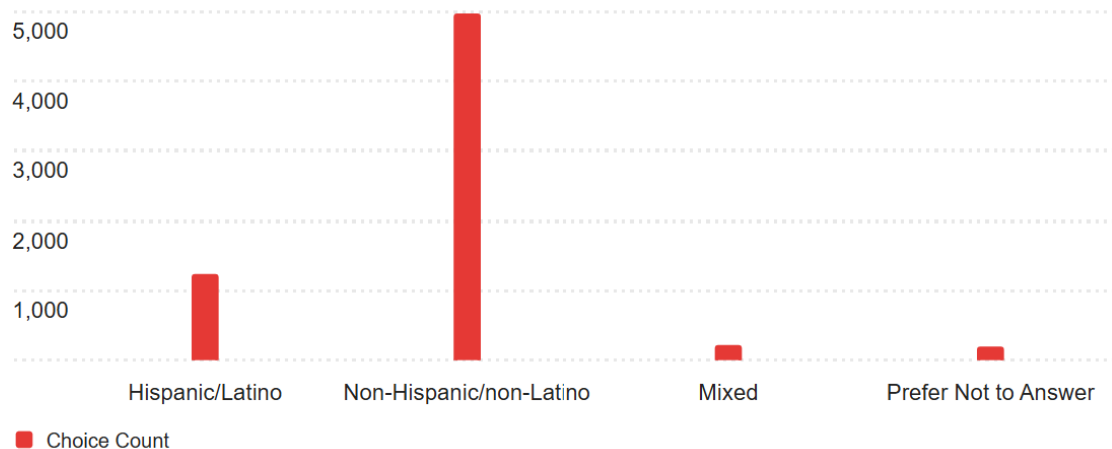
Q23 - Your Exact Age



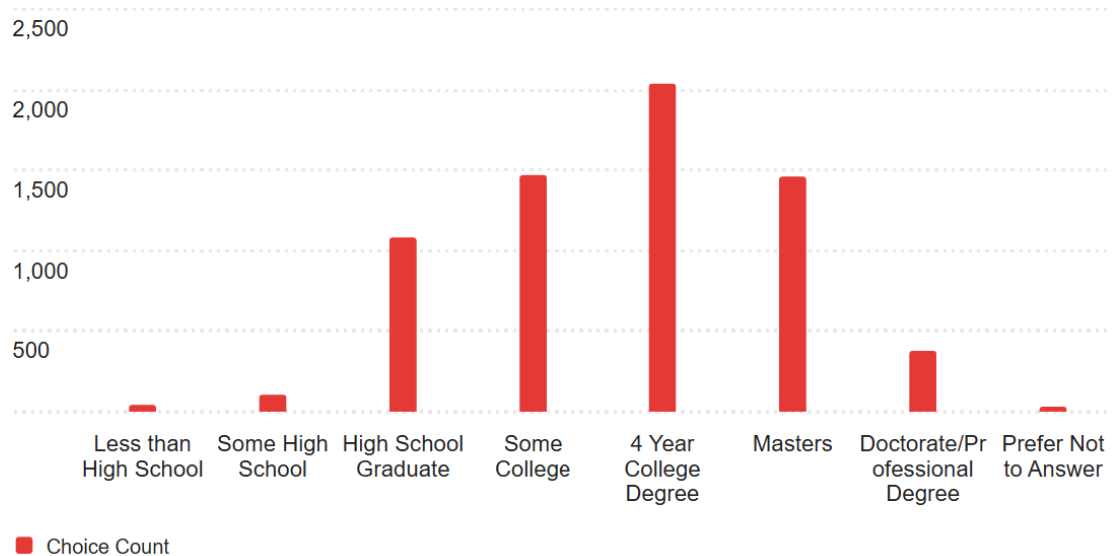
Q15 - Your Race



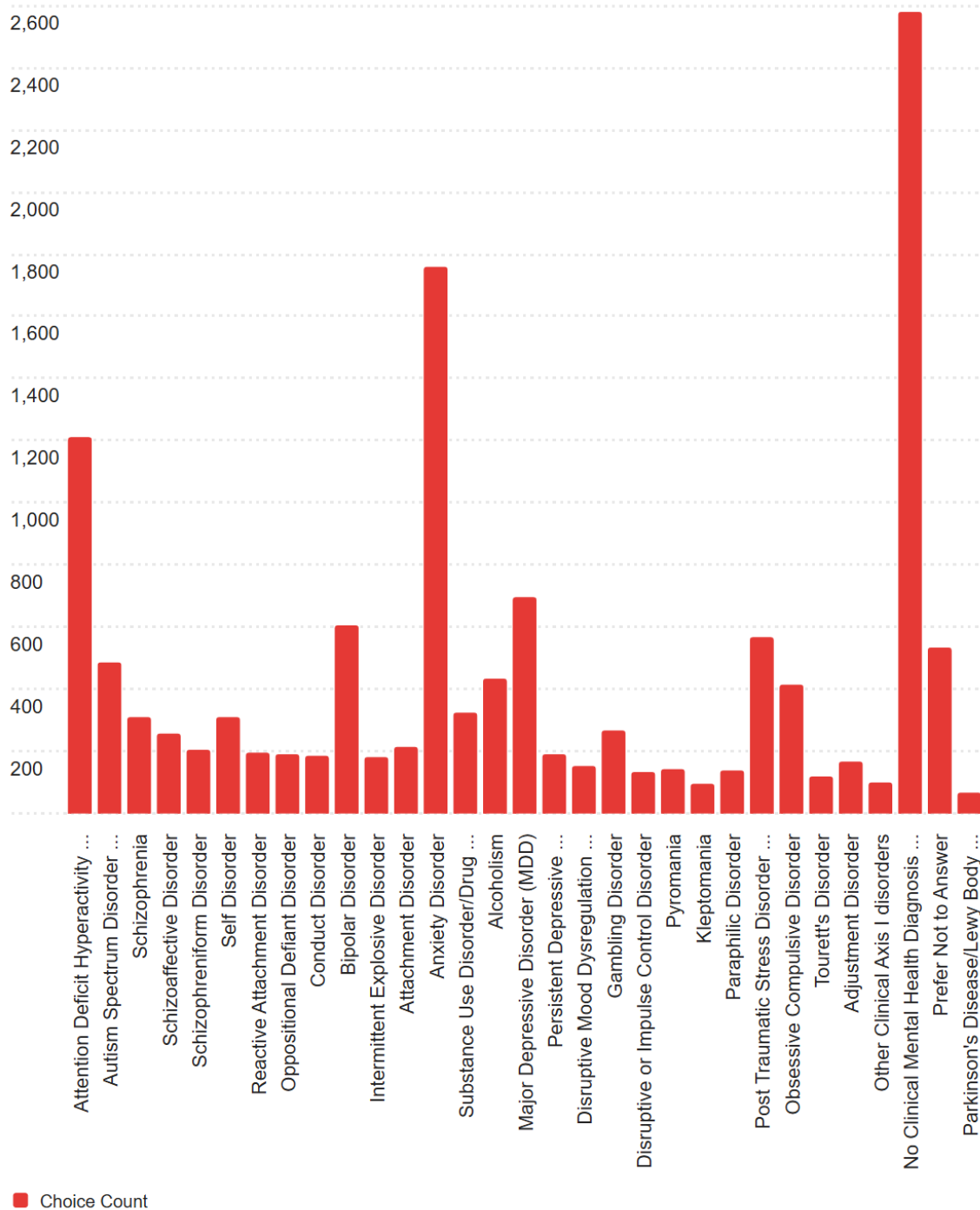
Q16 - Your Ethnicity



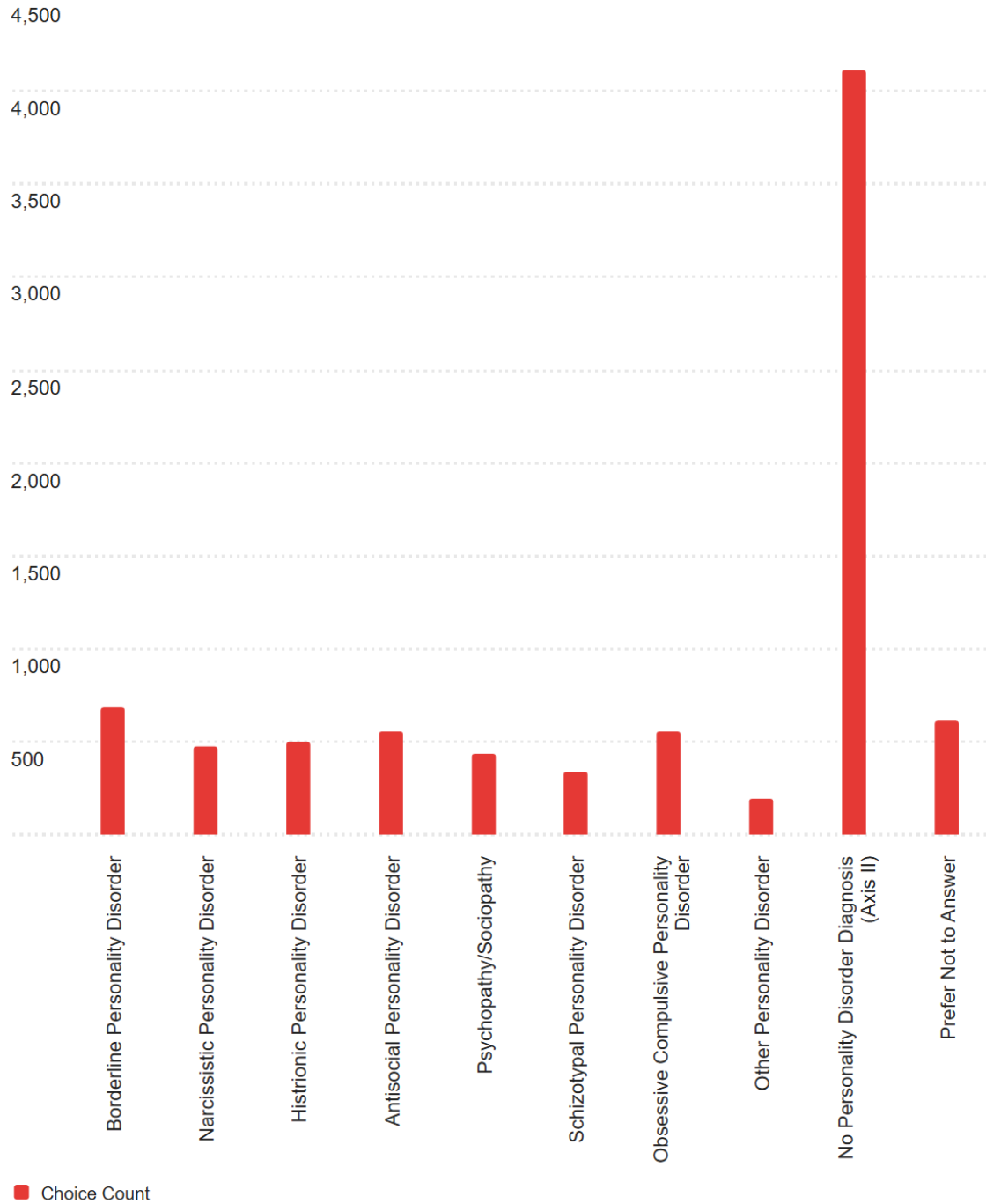
Q17 - Education Level



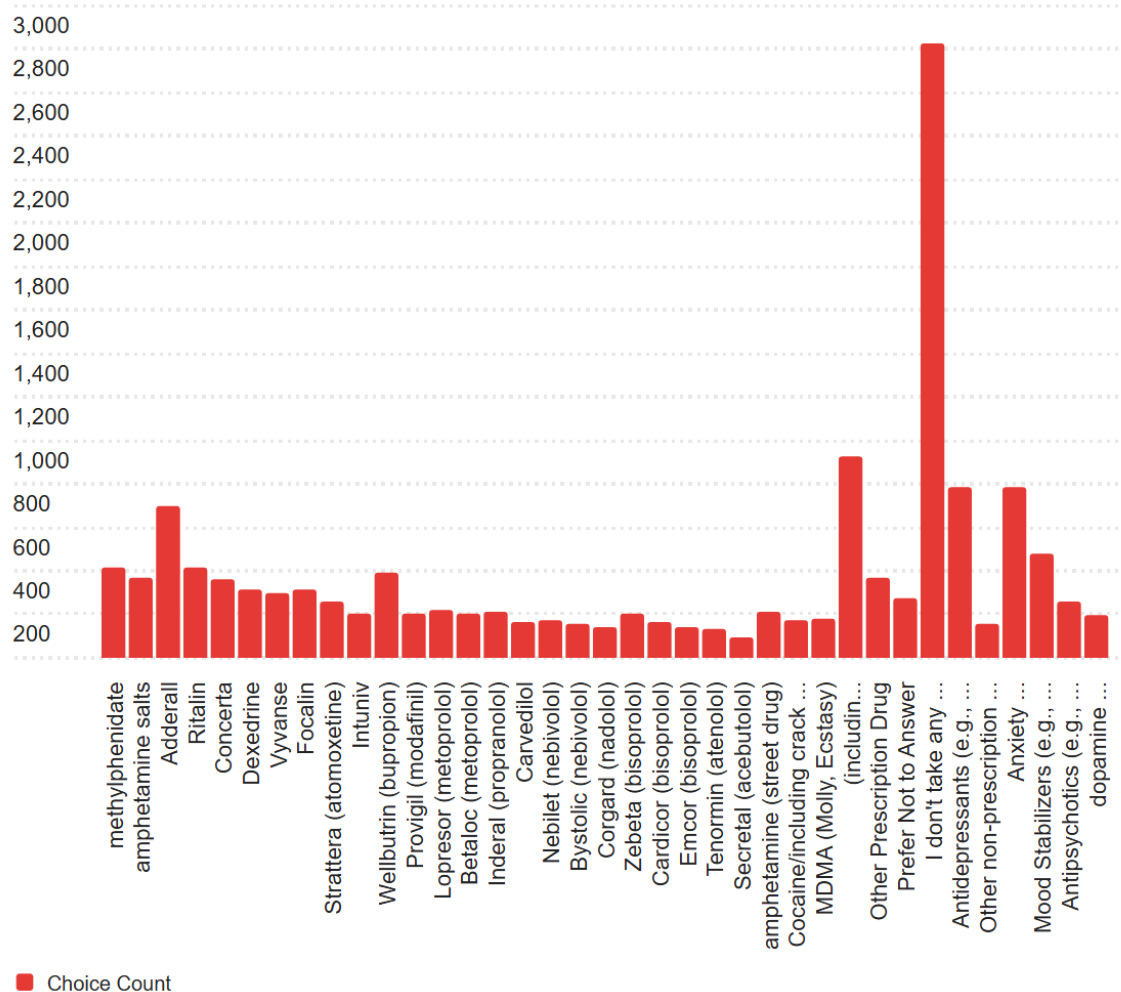
Q19 - Clinical Mental Disorders (also known as Axis I disorders), excluding personality disorders, or Parkinson's Disease.



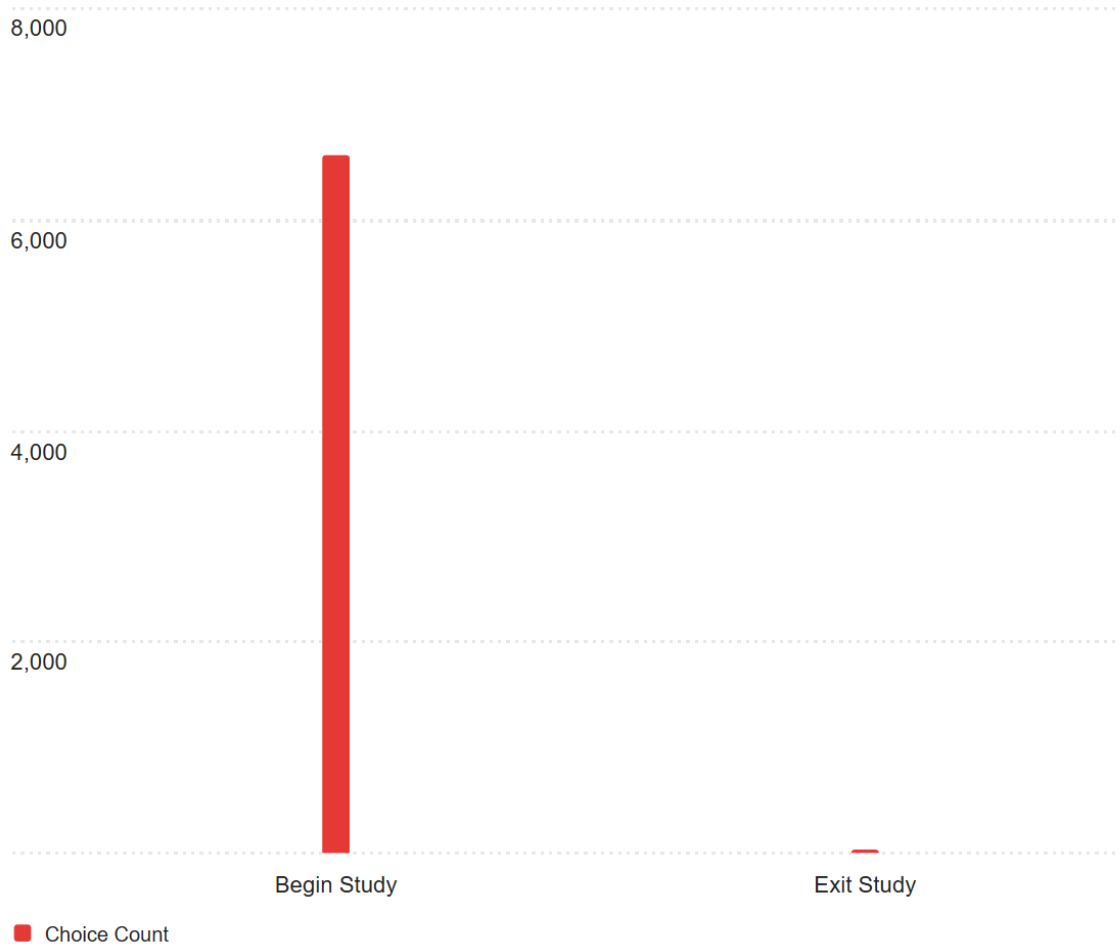
Q20 - Personality Disorders (also known as Axis II disorders) and related disorders, excluding clinical mental disorders (Axis I)



Q21 - The following questions related to any medications you are currently taking or drugs you are currently using. Click a box only if you have taken the drug within the past 24 hours. Do not click a box if you have taken the drug in the past, but have not taken the drug within the past 24 hours. Even though your responses are anonymous, these questions are optional, and are not required for you to complete this study. If you are not comfortable answering all the questions below, simply click 'prefer not to answer'. If you are not comfortable disclosing a specific drug, but are comfortable with others, simply do not click on the drug you prefer not to disclose. Click as many as apply to you:



Q22 - The testing portion of the study will start next. You will be asked to complete 4 measures. The first is a brief 30 question (3 minute) self-report measure. Then you will complete each of 3 interactive testing instruments (behavioral measures) ranging from 5-15 minutes each. PLEASE CAREFULLY FOLLOW THE INSTRUCTIONS FOR EACH MEASURE! IF YOU ARE NOT COMFORTABLE INSTALLING THE INQUISIT APP ON YOUR COMPUTER CLICK "Exit Study" IF YOU CANNOT COMPLETE ALL 4 INSTRUMENTS IN ONE SITTING of 20-40 MINUTES, click "Exit Study" To proceed, please click "Begin Study" and click the forward arrow. To withdraw from and exit the study click "Exit Study"



Appendix C

BIS-11

People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and click the appropriate response button. Do not spend too much time on any statement. Answer quickly and honestly.

1. I plan tasks carefully

☒ Rarely/Never
 ☐ Occasionally
 ☐ Often
 ☐ Almost Always/Always

2. I do things without thinking

☐ Rarely/Never
 ☐ Occasionally
 ☐ Often
 ☒ Almost Always/Always

3. I make-up my mind quickly

☐ Rarely/Never
 ☒ Occasionally
 ☐ Often
 ☐ Almost Always/Always

4. I am happy-go-lucky

☒ Rarely/Never
 ☐ Occasionally
 ☐ Often
 ☐ Almost Always/Always

5. I don't 'pay attention'

☒ Rarely/Never
 ☐ Occasionally
 ☐ Often
 ☐ Almost Always/Always

6. I have 'racing thoughts'

☒ Rarely/Never
 ☐ Occasionally
 ☐ Often
 ☐ Almost Always/Always

7. I plan trips well ahead of time

☐ Rarely/Never
 ☐ Occasionally
 ☒ Often
 ☐ Almost Always/Always

8. I am self-controlled

☐ Rarely/Never
 ☐ Occasionally
 ☐ Often
 ☒ Almost Always/Always

9. I concentrate easily

☐ Rarely/Never
 ☐ Occasionally
 ☐ Often
 ☒ Almost Always/Always

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10. I save regularly

☐ Rarely/Never
 ☐ Occasionally
 ☒ Often
 ☐ Almost Always/Always

11. I 'squirm' at plays and lectures

☐ Rarely/Never
 ☐ Occasionally
 ☒ Often
 ☐ Almost Always/Always

12. I am a careful thinker

☐ Rarely/Never
 ☒ Occasionally
 ☐ Often
 ☐ Almost Always/Always

13. I plan for job security

☒ Rarely/Never
 ☐ Occasionally
 ☐ Often
 ☐ Almost Always/Always

14. I say things without thinking

☐ Rarely/Never
 ☒ Occasionally
 ☐ Often
 ☐ Almost Always/Always

15. I like to think about complex problems

☐ Rarely/Never
 ☐ Occasionally
 ☒ Often
 ☐ Almost Always/Always

16. I change jobs

☐ Rarely/Never
 ☒ Occasionally
 ☐ Often
 ☐ Almost Always/Always

17. I act 'on impulse'

☐ Rarely/Never
 ☐ Occasionally
 ☒ Often
 ☐ Almost Always/Always

18. I get easily bored when solving thought problems

☒ Rarely/Never
 ☐ Occasionally
 ☐ Often
 ☐ Almost Always/Always

19. I act on the spur of the moment

☐ Rarely/Never
 ☒ Occasionally
 ☐ Often
 ☐ Almost Always/Always

20. I am a steady thinker

☒ Rarely/Never
 ☐ Occasionally
 ☐ Often
 ☐ Almost Always/Always

21. I change residences

☐ Rarely/Never
 ☒ Occasionally
 ☐ Often
 ☐ Almost Always/Always

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22. I buy things on impulse

☐ Rarely/Never
 ☒ Occasionally
 ☐ Often
 ☐ Almost Always/Always

23. I can only think about one thing at a time

☐ Rarely/Never
 ☒ Occasionally
 ☐ Often
 ☐ Almost Always/Always

24. I change hobbies

☐ Rarely/Never
 ☒ Occasionally
 ☐ Often
 ☐ Almost Always/Always

25. I spend or charge more than I earn

☐ Rarely/Never
 ☒ Occasionally
 ☐ Often
 ☐ Almost Always/Always

26. I often have extraneous thoughts when thinking

☐ Rarely/Never
 ☒ Occasionally
 ☐ Often
 ☐ Almost Always/Always

27. I am more interested in the present than the future

☐ Rarely/Never
 ☒ Occasionally
 ☐ Often
 ☐ Almost Always/Always

28. I am restless at the theater or lectures

☐ Rarely/Never
 ☐ Occasionally
 ☐ Often
 ☒ Almost Always/Always

29. I like puzzles

☐ Rarely/Never
 ☐ Occasionally
 ☒ Often
 ☐ Almost Always/Always

30. I am future oriented

☒ Rarely/Never
 ☐ Occasionally
 ☐ Often
 ☐ Almost Always/Always

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Appendix D

Go/No-Go Task (GNG)

Welcome to the Go / No-Go Task!

Please read these instructions carefully!

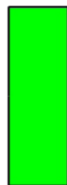
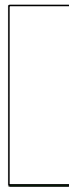
On each trial, a white rectangle will appear on the screen.
After a short time, the rectangle will either turn **green** or **blue**.

*Press the spacebar key as quickly as possible whenever the rectangle turns **green**.
If the rectangle turns **blue**, do not respond at all.*

Try to respond as quickly as possible while making as few errors as possible.

There'll be no practice. The task will take about 10 minutes to complete.
Once you begin, you cannot exit until you finish or until all trials complete if you stop responding.

Press the spacebar to begin.



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...

You have reached the end of the task.

Thank you!

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Appendix E

Stop Signal Task (SST)

Stop Signal Task

Please read these instructions carefully! Including those between sessions!

This is a reaction time task. It should take about 15 minutes to complete.

Your basic task will be to indicate the direction of an arrow by pressing a dedicated left or right response key.

However: if you hear a sound -called the Stop Signal-, STOP your response on that trial. Do NOT respond.

Turn your sound on and press SPACEBAR to hear the Stop Signal sound.



This is the Stop Signal.

If you didn't hear it clearly, adjust your volume and press 'R' to repeat this trial. Otherwise, press 'C' to continue with the instructions.

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Stop Signal Task

On each trial you will see an arrow pointing left or right. Your task is to indicate the direction of the arrow, responding as quickly and accurately as possible:

Press the left ('D') key when the arrow points left.

Press the right ('K') key when the arrow points right.

Sometimes a sound called the Stop Signal plays AFTER the arrow appears. If you hear the Stop Signal, STOP your response on that trial.

Sometimes the Stop Signal will play just after the arrow appears, making it easier to stop your response. Other times, it will play later after the arrow, making it more difficult to stop.

Nevertheless, DO NOT WAIT for the stop signal. If you wait, stop signals will only play later in the next trials and the task will get HARDER.

Press SPACEBAR to start a practice session.

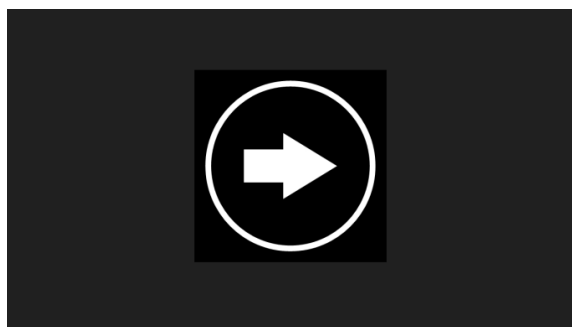
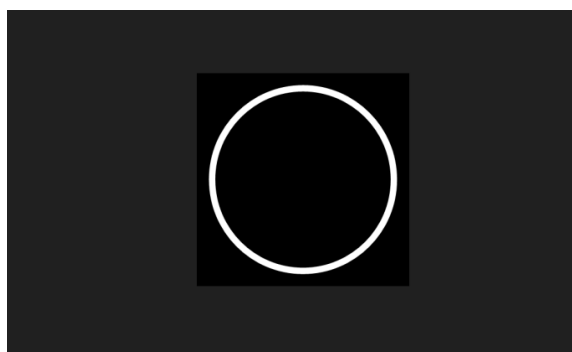
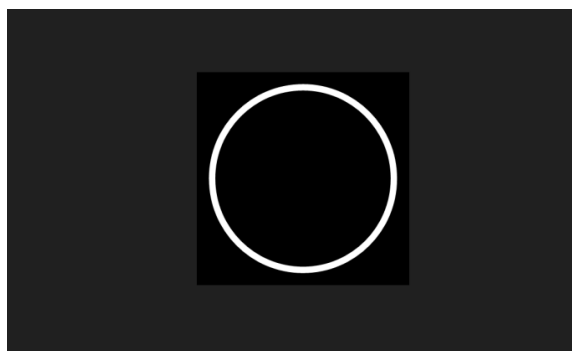
First, some practice.

Press <Spacebar> to start.

Get Ready:

Place your fingers on the D and K keys

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...

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00:01**RESULTS BLOCK PRACTICE**

Error Responses:	19
% Correct Responses:	20%
Average Response Time:	48 ms
Stop Signals Errors:	4
% Correct Stop Signals:	50%

Practice is over. Now the test phase will begin.

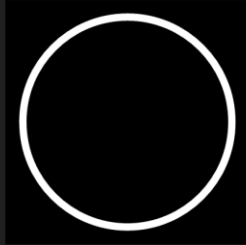
DO NOT WAIT for the stop signal. If you wait, stop signals will only play later in the next trials.

Press <Spacebar> to start..

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Get Ready:

Place your fingers on the D and K keys



...

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00:01**RESULTS BLOCK 1**

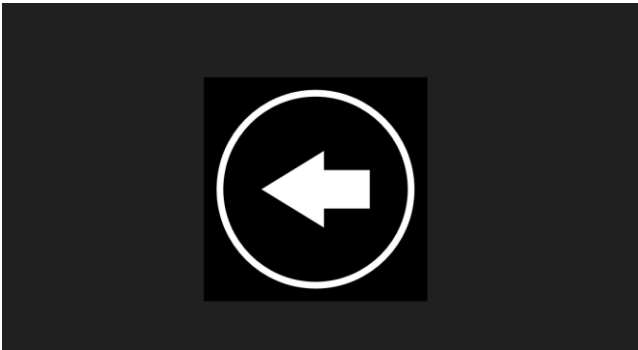
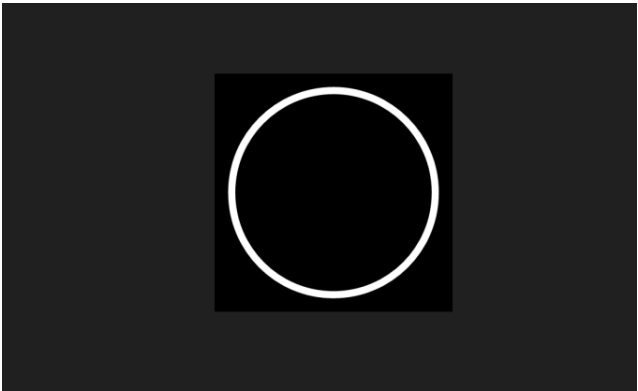
Error Responses:	40
% Correct Responses:	25%
Average Response Time:	52 ms
Stop Signals Errors:	10
% Correct Stop Signals:	44%

Get Ready:

Place your fingers on the D and K keys

DO NOT WAIT for the stop signal. If you wait, stop signals will only play later in the next trials.

Press <Spacebar> to start.



...

00:01

RESULTS BLOCK 2

Error Responses:	35
% Correct Responses:	35%
Average Response Time:	55 ms
Stop Signals Errors:	11
% Correct Stop Signals:	38%

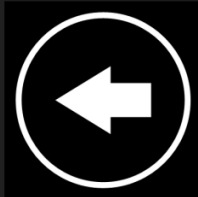
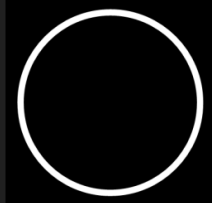
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Get Ready:

Place your fingers on the D and K keys

DO NOT WAIT for the stop signal. If you wait, stop signals will only play later in the next trials.

Press <Spacebar> to start.



...

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00:01**RESULTS BLOCK 3**

Error Responses:	36
% Correct Responses:	33%
Average Response Time:	51 ms
Stop Signals Errors:	12
% Correct Stop Signals:	33%

Thank you!

<press spacebar to exit>

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Appendix F

Wisconsin Card Sorting Test (WCST)

Card Sorting Task

Please read these instructions carefully! This task should take about 5 minutes.

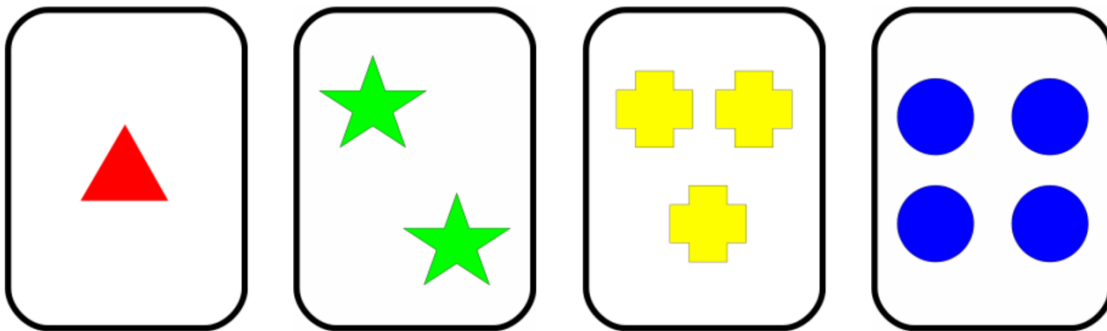
You are given two decks of cards, each containing 64 cards.

You will be given one card at a time and you are asked to sort it into one of four piles.

You place a card into a pile by clicking on one of the four cards that you see below.

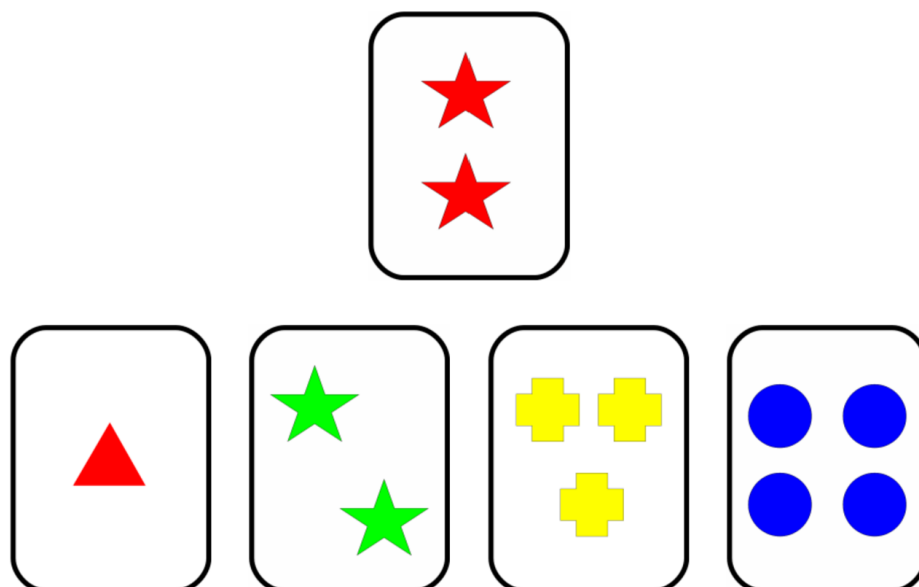
When you put the card into the correct pile, the word 'correct' will appear on the screen.
But if you put the card into the wrong pile, the word 'wrong' will appear.

The goal is to get as many cards into the correct pile as possible.

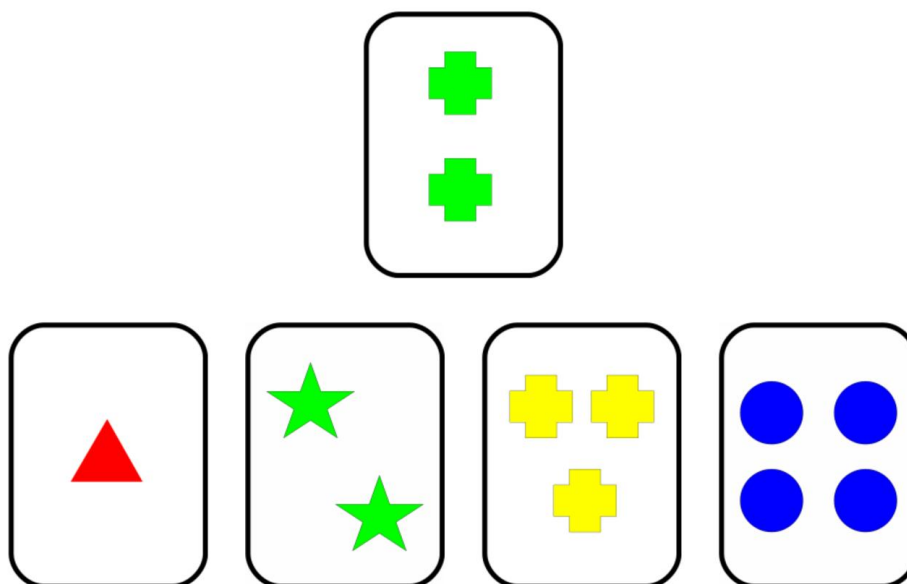


START

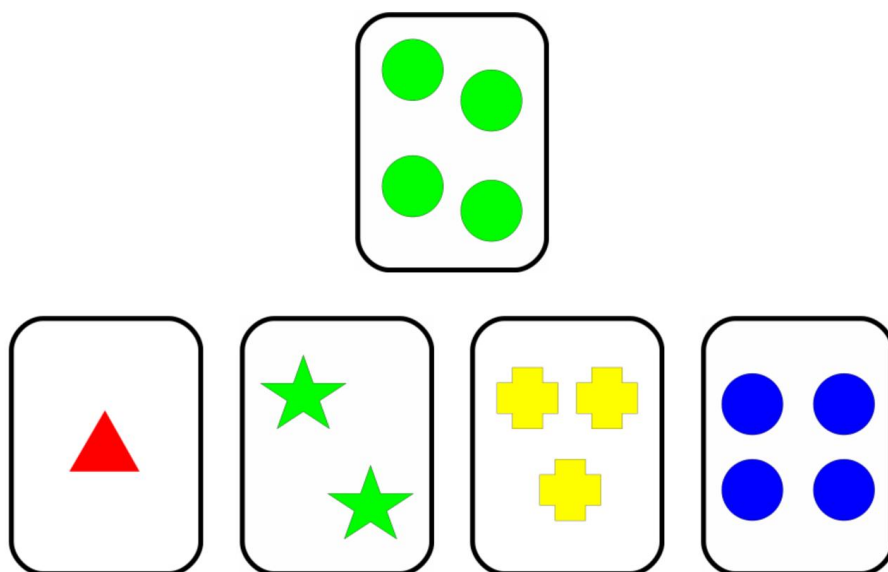
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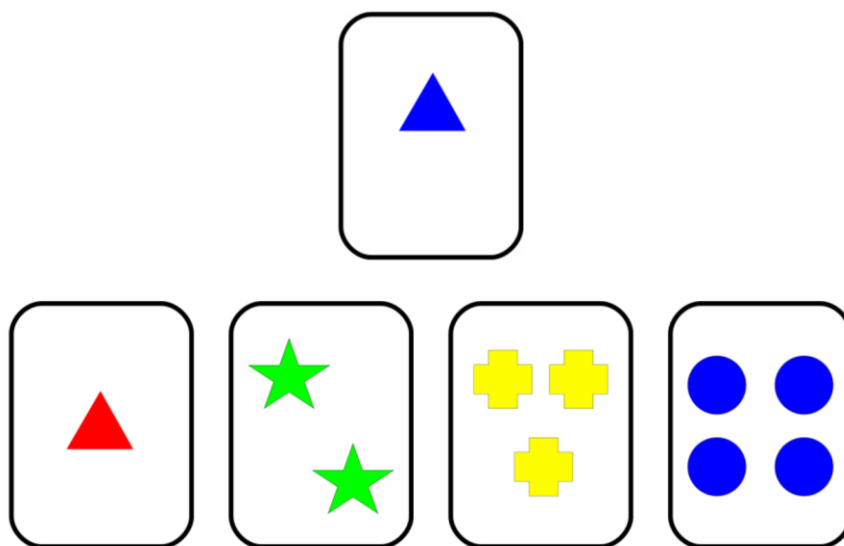
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