EFFORT-BASED DECISION MAKING AND PSYCHOPATHOLOGY IN CHILDREN AND ADULTS: AN RDOC STORY

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A Dissertation in Neuroscience

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Approved ____________________________
(Sponsor’s signature)

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Abstract

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The Research Domain Criteria (RDoC) initiative was introduced by the National Institute of Mental Health as a new research framework aimed at addressing longstanding pitfalls within the field of psychiatric research. This framework focuses on the study of fundamental units of human psychological behavior across multiple levels of information to inform our understanding of psychopathology. These units are categorized into larger domains of similar function, such as the Positive Valence Systems domain, which encompasses aspects of human reward-related behavior. This dissertation centers on the ‘effort’ component of human reward behavior, defined as the moderating effect of the perceived costs of physical or cognitive requirements on the valuation of a reinforcer.

Three studies are presented from a program of research spanning five years on the study of ‘effort’ utilizing the RDoC research framework from both a behavior and genetics perspective. The first study (Chapter 2) is an exploratory study with the first application of RDoC to the study of ‘effort’ in relation to psychopathology in children and adults. It finds that behavioral measures of ‘effort’ in children and adults were associated with specific types of psychopathologies and with differing profiles between sexes. The second study (Chapter 3) assesses the cross-generational stability, divergent validity, and replicability of ‘effort’ and its associations with psychopathology in children and adults. It finds that ‘effort’ has divergent validity from other RDoC constructs of reward behavior, and that the specific associations with psychopathology initially observed in the
first study were replicated in a larger population. It also finds that ‘effort’ does not
display cross-generational stability between children and their parents. The third study
(Chapter 4) examined the genetic contributions to ‘effort’, and the moderating effect of
‘effort genes’ on psychopathology. It found that genetic loci on three different
chromosomes had genome-wide significant associations with quantitative measures of
‘effort’, and that polygenic risk scores generated from these measures were significant
predictors of parent-reported levels of psychopathology in children. Together, this
program of research provides the first comprehensive application of RDoC to the study of
effort-based behavior and psychopathology in children and adults and has important
implications for the advancement of the RDoC framework and future research in this
area.
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My Brianna

Bri, thank you so much for the constant and consistent love and support throughout this whole endeavor. It is from you and for you that I drew the strength to be able to overcome the biggest obstacles and toughest challenges to progress towards our brightest future. I am, without a doubt, a better person, better researcher, and better student because of you, and this accomplishment is a reflection of all the good we bring together. This achievement is because of you, for you, and is all the more meaningful shared alongside you.

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To my grandfather, for whom I began this entire journey in the first place. I know that your last few years were not the kindest as you fought back against the Alzheimer’s
disease that tried to rob you of your memories and personhood, but I will never forget the warm smile and radiant happiness on your face each and every time I came to visit to sit with you and tell you about how my school was going. And I could not help but feel the intensity of your pride in me when I told you that I was working towards becoming a doctor. This accomplishment means as much to you as it does to me, and I know that you’re smiling at my success from wherever you are.

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Chapter 1: Introduction

The Current State of Psychiatric Diagnostic Systems

The field of psychiatry at present has three different major classification systems. The Diagnostic and Statistical Manual of Mental Disorders (DSM) published by the American Psychiatric Association has long been the pillar around which modern mental health research has revolved. The Mental and Behavioral Disorders section of the International Classification of Diseases (ICD) developed by the World Health Organization (WHO) has seen longstanding wide usage in clinical psychiatric settings, owing to its greater emphasis on public health applications relative to the DSM. Together the DSM and ICD have represented the de facto standard for psychiatric research and clinical practice, and although both have undergone multiple revisions, significant unresolved criticisms and shortcomings imply the need for more than simple review and updating (Phillips et al., 2012). The Research Domain Criteria (RDoC) initiative put forth by the National Institute of Mental Health (NIMH) in 2009 is the newest system of the three and seeks to provide a markedly different approach for the continued development of diagnostic criteria.

Both the DSM and ICD systems are primarily concerned with the signs and symptoms of mental illness and rely on collections of these to define specific psychiatric disorders (P. R. McHugh, 2005). This focus on diagnoses makes functional sense, as in medicine a diagnosis serves as a determination of the exact nature of patient’s disease to then direct optimal treatment choice. Effective treatments for mental disorders do exist, in no small part to research conducted under the guiding umbrella of the DSM and ICD systems. Multiple modalities – pharmaceutical interventions, medical devices, psychosocial/behavioral treatments – have been established for many major classes of disorders such as anxiety, depression, bipolar disorder, and schizophrenia.
(Bahji, Ermacora, Stephenson, Hawken, & Vazquez, 2020; Bighelli et al., 2021; Gartlehner et al., 2017). However, these treatments lack precision, and are utilized across broad classes of disorders. Anti-psychotic medications are administered for treatment of schizophrenia, bipolar disorder, and personality disorders (Harrison et al., 2016; Stoffers et al., 2010). Anti-depressant agents like selective serotonin reuptake inhibitors are used for not only depression, but also a wide variety of anxiety and mood disorders (Golden, 2004; Thibaut, 2017). Behavioral interventions originally designed for the treatment of a specific type of disorder have been generalized to almost any kind of mental disorder, as is the case with cognitive-behavioral therapy (originally for internalizing disorders) (Sensky et al., 2000). This lack of specificity among psychiatric treatments calls into question the legitimacy of current diagnostic definitions. If it is understood that pharmacological interventions function by affecting discrete biological processes, and such biological processes are shared between different disorders to the extent that they are responsive to treatment, can the different disorders truly be considered diagnostically distinct?

Imprecision among psychiatric treatments is unfortunately not the only issue stemming from the current systems. Treatment development research conducted in terms of DSM and ICD diagnoses has been hindered by a host of problems, including excessive co-morbidity of disorders, as well as heterogeneity of mechanisms and reification of disorders (Hyman, 2010; Kendell & Jablensky, 2003). In fact, a report by pharmaceutical industry scientists stated that on average, a marketed psychiatric drug was only efficacious in about half of patients receiving it, and explicitly attributed the low response rate to artificial grouping of heterogenous syndromes with differing pathophysiological mechanisms into single disorders (Wong, Yocca, Smith, & Lee, 2010). The withdrawal of many pharmaceutical companies from active psychiatric
treatment development research because of these problems is a striking indicator of the degree of their severity (Abbott, 2010; Miller, 2010). Although revisions have continued and updates have been made as recently as March 2022 (American Psychiatric Association, 2022), it is unlikely that some of these intrinsic obstacles have been sufficiently addressed.

Contrasting the improvements in disease burden for other types of diseases over the past several decades with those of mental disorders demonstrates how the field of psychiatric research has fallen behind the rest of medicine. A classic example of this is the marked impact of research on heart disease mortality. Projected deaths based on climbing rates between 1950 and 1968 for heart disease predicted more than 1.8 million deaths in 2010, but due to the rapid progress of research, actual mortality was only less than a quarter of that number (NHLBI, 2012). Similarly, survival rates for children with acute lymphoblastic leukemia have improved from less than 10% in the 1960s to over 90% by the mid-2000s (Hunger et al., 2012). Other areas of medicine have honed the definitions of diseases to contain precise specification of the genetic, molecular, and cellular aspects of disease. With cancer in particular, diagnosis in many cases go beyond simply the involved organ(s) or a pathology report, but rather analysis of genetic variants that can predict the optimal treatments (Lamberti, Wilkinson, Peña, Getz, & Beltre, 2012). This new individualized treatment approach has been termed ‘precision medicine’, and draws from an integrated understanding of the underlying pathology and biological mechanisms that make disease entities distinct (König, Fuchs, Hansen, von Mutius, & Kopp, 2017). In contrast to all of these, prevalence and mortality rates for mental illness remain unchanged, no biological or cellular clinical tests for diagnosis exist, disorder detection lags well behind generally accepted onset of pathology, and no well-developed preventative interventions have been able to be formulated (Cuthbert & Insel, 2013; Kessler et al., 2005). The wealth of new knowledge in basic
neuroscience and rapid advancement in technology are in dire need of a new framework through which they can be integrated to better inform research efforts and diagnostic definitions (Hyman, 2007; Sanislow et al., 2010). It is this need that the NIMH developed the RDoC project to address, and an understanding of the context in which RDoC stands in the field of psychiatry is a critical component and central core of each study within this dissertation.

Research Domain Criteria: Fundamental Constructs for Psychopathology Research

RDoC at its base is a paradigm shift away from the traditional view of mental health disorders as symptom complexes based primarily on clinical descriptions. The NIMH has stated that its overarching goal is to ‘develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures’ (NIMH, 2008). To this end, RDoC first strives to identify the fundamental, primary behavioral functions of the brain, and specify the biological mechanisms and neural systems that drive implementation of these functions. An internal NIMH working group established a hierarchical scheme, with specific dimensions of function nested within six major domains. A series of workshops convened 30 to 40 experts from across the field of mental health research per domain to determine which dimensions should be included within the domain; provide a definition for each dimension; and provide a list of elements for each dimension that could be used to measure it at each of several units of analysis (Cuthbert & Insel, 2013). These dimensions were explicitly defined as dependent upon continued research to refine and evolve scientific understanding of their function and implementing circuits, subject to further validation and revision. As such, the dimensions are termed ‘constructs’ as classically defined in psychological research (Maccorquodale & Meehl, 1948). The result of these work groups’ effort was organized into the
RDoC ‘matrix’ consisting of a series of rows, with constructs nested within superordinate domains, and columns representing units of analysis (See example, **Table 1.1**).

**Domain:** Positive Valence Systems  
**Construct:** Reward Learning

<table>
<thead>
<tr>
<th>Genes</th>
<th>Molecules</th>
<th>Cells</th>
<th>Circuits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Various genes involved in dopamine synthesis, clearance, and receptor signaling; plasticity-related genes CREB, FosB; Synapse-related genes; Epigenetic factors (HDAC, methyl transferases, etc.); DARP32; COMT; NMDA receptors on D1 neurons; Adenyl cyclase</td>
<td>dopamine &amp; dopamine-related molecules; acetylcholine; Co-released neuromodular glutamate</td>
<td>medium spiny neurons; dopaminergic neurons</td>
<td>dorsal striatum; Ventral striatum; Medial prefrontal; OFC; VTA/SN; Amygdala</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physiology</th>
<th>Behavior</th>
<th>Self-Reports</th>
<th>Paradigms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Error related negativity; Correct related negativity; Feedback related negativity; Midline theta</td>
<td>Approach behaviors; Consummatory behaviors toward any goal object</td>
<td>Ecological momentary assessment; Ambulatory assessment and monitoring</td>
<td>probabilistic reinforcement learning; deterministic reinforcement learning; Pavlovian conditioning; Instrumental conditioning and all its variants; Prediction error tasks</td>
</tr>
</tbody>
</table>

**Table 1.1** Snapshot of Reward Learning Construct from RDoC Matrix Version 1 (3/7/2016). 8 columns representing units of analysis have been split across 2 rows for readability.

When the RDoC matrix was under initial construction, information listed in the “Genes” column was drawn from the findings of candidate gene studies that had already been conducted at that time. In May of 2017, however, the NIMH work group removed references to specific genes in
the “Genes” column of the RDoC matrix, citing the need for more robust evidence of association from adequately powered genome-wide association studies (NIMH, 2017).

Within the RDoC system, the present dissertation concerns itself with the Positive Valence System (PVS) domain, defined by constructs primarily responsible for responses to positive motivational situations or contexts, such as reward seeking, consummatory behavior, and reward/habit learning (NIMH, 2018). The PVS domain was reorganized in 2018 by the NIMH Changes to the RDoC Matrix (CMAT) Council Workgroup to make the component constructs more straightforward and less redundant, and to more closely align with research in reinforcement learning, reward prediction errors and response to reward (National Institute of Mental Health, 2018). The PVS as currently defined is composed of three constructs: ‘reward responsiveness’, ‘reward learning’, and ‘reward valuation’, each of which is further subdivided into specific subconstructs (Table 1.2). ‘Reward responsiveness’ (RR) is defined as the processes that govern an organism’s hedonic response to impending or possible reward, the receipt of reward, and following repeated receipt of reward. It primarily reflects neural activity to reward cues and receipt of reward and can be measured in terms of subjective and behavioral responses. ‘Reward learning’ (RL) is considered a type of reinforcement learning and is defined as the process by which organisms acquire information about stimuli, actions, and contexts that predict positive outcomes, and by which behavior is modified when a novel reward occurs, or outcomes are better than expected. ‘Reward valuation’ (RV) is defined as the processes by which the probability and benefits of a prospective outcome are computed by reference to external information, social context, and/or prior experience. These computational processes are influenced in particular by preexisting biases, learning, memory, stimulus characteristics, and deprivations states (NIMH, 2018).
Table 1.2. Positive Valence System reorganization and components.

The RV construct contains three elemental components: ‘reward (probability)’, ‘delay’, and ‘effort’. ‘Reward (probability)’ is defined as the process by which the value of a reinforcer is computed as a function of its magnitude, valence, and predictability. ‘Delay’ refers to the modulating impact of the time interval prior to expected delivery of a reinforcer on the computational process of ‘reward (probability)’. Similarly, ‘effort’ refers to the modulating impact of the perceived costs of the physical or cognitive actions required to obtain a reinforcer (NIMH, 2018). Although elements from multiple PVS constructs are discussed and utilized in studies within this dissertation, the main focus is here on this ‘effort’ subconstruct of RV.

**Effort: An Elemental Unit of Human Reward Behavior**

Under the RDoC framework, ‘effort’ is an elementary component of the complex system that is human reward behavior. Although the studies within this dissertation discuss reward behavior as a whole, as well as other non- ‘effort’ components, the analytical focus of Studies 1-
3 is on ‘effort’ as a quantifiable, measurable point of study. While it is indeed relevant to understand the larger context of reward behavior and all the underlying processes that constitute it, especially in relation to psychopathology or psychiatric symptoms, we chose specifically to constrain the analytical side of our investigations to ‘effort’ alone. Given that a main goal of RDoC is to build knowledge upward by starting at the fundamental units of behavioral functions (Cuthbert & Insel, 2013), it is therefore well-aligned with this goal to conduct focused research on ‘effort’, to understand how aberrations and abnormalities in its function then relate to psychopathological presentation. This analysis then feeds into the larger discussion of reward behavior and reward-related psychopathology. Our approach can be considered analogous to how non-psychiatric research attempting to study a particular biological/functional pathway would conduct and design studies to investigate a specific cellular component (e.g., a cell-surface receptor).

‘Effort’ as a concept has been studied in connection with many different forms of mental illness and is known to be impacted in multiple major disorders, including anxiety, depression, schizophrenia, and autism spectrum disorders. In non-psychiatric individuals, different levels of reward stimulate behavior to different degrees, such that individuals tend to exert more effort to obtain greater rewards (Pessiglione et al., 2007; Robinson, Yager, Cogan, & Saunders, 2014). A recent behavioral and imaging study of effort allocation in individuals diagnosed with an anxiety disorder found that, in comparison to low-anxiety individuals, high-anxiety individuals expended both greater effort when presented with higher incentives and lower effort when presented with lower incentives. These findings were mirrored in the EEG measurements, where increased activity in the anterior cingulate cortex (ACC) was observed at the high incentive level and increased activity in the posterior cingulate cortex (PCC) at the low incentive level (Berchio,
Rodrigues, Strasser, Michel, & Sandi, 2019). Neurons of the ACC are known to be involved in reward responsiveness processing, whereas PCC neurons are typically associated with resting conditions or nonengaging tasks (Bush et al., 2002; Leech & Sharp, 2014). In contrast, a study of effort allocation in major depressive disorder (MDD) found that participants with MDD were less willing to expend effort for the opportunity to earn larger monetary rewards as compared to healthy controls. Additionally, they found that the duration of a participant’s major depressive episode was predictive for reduced effort expenditure at high reward levels, suggesting that motivational deficits are associated with higher MDD severity (Treadway, Bossaller, Shelton, & Zald, 2012).

Similar deficits in motivation and effort expenditure have been observed in studies of schizophrenia. Behavioral and imaging results have indicated that the severity of such deficits relates to the ability to precisely represent and flexibly update the value of both rewards and the costs of obtaining them (Gold et al., 2013a; Morris, Quail, Griffiths, Green, & Balleine, 2015; Waltz & Gold, 2016). With respect to autism spectrum disorders, previous literature has demonstrated that individuals with these disorders display greater willingness to expend effort for rewards irrespective of reward probability and magnitude (Damiano, Aloï, Treadway, Bodfish, & Dichter, 2012). Multiple studies have found that this abnormal effort allocation is characterized by impaired usage of contextual information (De Martino, Harrison, Knafo, Bird, & Dolan, 2008; Johnson, Yechiam, Murphy, Queller, & Stout, 2006; Pellicano et al., 2011). These studies conducted from a traditional, DSM/ICD-based approach have established a consistent association between abnormal effort function and psychopathology as defined by those systems. Given this wide array of disorders, studies within the current dissertation sought
to examine and characterize the relationship between ‘effort’ and psychopathology in a broader, more RDoC-aligned nature.

In the studies within this dissertation, quantitative measures of ‘effort’ were obtained via the Effort Expenditure for Rewards Task (EEfRT), a paradigm for effort-based decision-making. While a more detailed description of this task can be found in the ‘Materials and Methods’ sections of **Chapters 2-4**, EEfRT can briefly be described as a multi-trial game in which subjects choose between performing a “hard-task” or an “easy-task” to earn varying amounts of monetary rewards (Figure 1.1). The EEfRT generates two quantitative outcomes: hard task choice percentage, which represents an individual’s willingness to expend effort; and reward sensitivity, which represents the degree to which changes in reward magnitude influence an individuals’ willingness to expend effort (Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009). The EEfRT is currently the only NIMH-endorsed behavioral paradigm for the study of the RDoC ‘effort’ construct (NIMH, 2016).
Figure 1.1. Schematic diagram of a single trial of the Effort Expenditure for Rewards Task (EEfRT). (A) Subjects begin by seeing a 1 second fixation cue. (B) 5 second choice period in which subjects are presented with information regarding reward magnitude the hard and easy tasks and probability of receiving any reward for that trial. (C) 1 second ‘ready’ screen. (D) Subjects make rapid button presses to complete the chosen task (easy task – 7 seconds, hard task – 21 seconds). (E) Subjects receive feedback on whether they have successfully completed the task or not. (F) Subjects receive reward feedback as to whether they received any money for the trial and what amount.

Present Investigation

The present investigation is a multi-method program of research examining the construct of ‘effort’ as defined by the RDoC project and its relationship with psychopathology in children and adults. The three studies that make up this dissertation employ behavioral task and self-report analyses (Study 1 and Study 2), genome-based analyses (Study 3), and a family study design to understand and characterize the phenomena of interest from multiple methodological perspectives. This study design was chosen specifically because, at the time of inception, the RDoC project was new and in need of validation. To this end, the grant under which these studies were funded proposed an application of an updated version of the validation framework of Robins and Guze (Robins & Guze, 1970). Under this framework, we aimed to assess construct reliability, coherence, divergent validity, developmental stability (across generations if not within subjects over time), associations with psychopathology, and familiality (genetic basis). The findings obtained by these studies could then be used to advance our knowledge of human reward behavior, inform future research endeavors relating reward and psychopathology, and provide critical feedback and evaluation of the RDoC system (Faraone & Glatt, 2014).
The first study (Chapter 2) is an assessment of the associations between quantitative behavioral measures of ‘effort’ and dimensions of psychopathology, to establish as a baseline that the RDoC construct of ‘effort’ was relevant in psychiatric research. ‘Effort’ was found to be significantly associated with dimensions of psychopathology in both adults and children in concordance with existing literature. These associations were sex-specific, similar to findings in the literature, but did not have familial consistency, which indicated the need for further investigation. The second study (Chapter 3) is an empirical validation of ‘effort’ as divergent from other components of reward behavior, a deeper investigation into the familiality (or lack thereof) of ‘effort’, and a replication of association models in a larger participant population. ‘Effort’ demonstrated divergent validity from other RDoC PVS constructs, and associations between ‘effort’ and dimensions of psychopathology found in Study 1 remained consistent even in the larger population. Quantitative measures of ‘effort’ were not found to be correlated between parents and their children, raising important points of discussion for future revisions to the RDoC framework. The third study (Chapter 4) sought to investigate the genetic basis of ‘effort’ and its relationship with psychopathology, through genome-wide association analyses, gene-set enrichment analysis, and association models using polygenic risk scores. Three single nucleotide polymorphisms were found to be genome-wide significant in their association with psychopathology. Enrichment analysis demonstrated that multiple gene sets drawn from biological pathways known to be involved in reward were associated with quantitative behavioral measures of ‘effort’. Lastly, polygenic risk scores were found to be predictive for the same dimensions of psychopathology associated with behavioral measures of ‘effort’ in adults and children that were found in studies 1 and 2.
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Chapter 2: Study One - An Initial RDoC-based Exploration of Effort and Psychopathology in Children and Adults

Note: The following chapter contains excerpts from a manuscript previously published in Psychological Medicine. The citation for that article is as follows:


However, please note that to fit the overall flow of the dissertation that the manuscript has been edited and updated from the original publication for greater clarity and contextualization. As the primary author on this manuscript, I was responsible for the entirety of the analysis, data interpretation, and the overwhelming majority of the writing of the manuscript, including figure and table creation. Sarah Van Orman, Pat Forken, Steven Blatt, and Wanda Fremont contributed to the actual collection of the data. Avery Albert, Stephen Glatt, and Stephen Faraone provided feedback on analytical methods and also contributed some finalizing edits to the writing of the manuscript.
Introduction

The RDoC Positive Valence Systems domain that was conceived in the original RDoC initiative was composed of five constructs rather than the current three. These original five constructs were Approach Motivation (AM), Initial Responsiveness to Reward Attainment (IRRA), Sustained Responsiveness to Reward Attainment (SRRA), Reward Learning (RL), and Habit. As defined in the original RDoC matrix, the AM construct was broken up into four subconstructs: ‘reward valuation’, ‘effort valuation’, ‘reward prediction error’, and ‘preference-based decision-making’ (Cuthbert, 2014). This old AM construct is most analogous to the current Reward Valuation (RV) construct, although there are distinct differences in their exact compositions. Most importantly, however, the old ‘effort valuation’ subconstruct of AM that is the subject of this chapter directly corresponds to the new ‘effort’ subconstruct of Reward Valuation, in terms of both definition and NIMH-endorsed methodologies of study (National Institute of Mental Health, 2018). Throughout this chapter, references to the ‘effort valuation’ subconstruct of AM can be taken to refer to the ‘effort’ subconstruct of RV, that was defined and explained in Introduction.

‘Effort valuation’ is a subconstruct of human psychological behavior that is defined as the processes by which the cost(s) of attaining an outcome is computed, and the tendency to overcome those response costs to obtain a positive reinforcer (NIMH, 2016). Previous research regarding the role of ‘effort valuation’ in psychopathology has consistently found differences in effort-based decision-making between participants with mental disorders and healthy comparison subjects. Behavioral studies examining specific disorders have each previously discovered significant links between measures of effort valuation and symptoms of psychopathology. For example, a study examining reward motivation in major depressive disorder (MDD) found that
MDD participants are less willing to expend effort for rewards and are less effective in their use of information about the magnitude and probability of rewards to guide choice behavior as compared to healthy controls (Treadway et al., 2012). In autism spectrum disorders (ASDs), research has revealed a relationship between inefficient effort-based decision-making and repetitive behavior symptoms in individuals with ASD. Affected individuals were more willing to expend effort to obtain a reward regardless of differences in reward value and probability (Damiano et al., 2012). Multiple studies investigating ‘effort valuation’ in schizophrenia have noted impaired effort allocation as a consistent finding in individuals with the disorder relative to healthy comparison participants (McCarthy, Treadway, Bennett, & Blanchard, 2016; Treadway, Peterman, Zald, & Park, 2015). These research findings suggest that measures of ‘effort valuation’ could be useful predictors of psychiatric disorder; yet it remains unclear if ‘effort valuation’ relates to specific diagnoses or to dimensions of psychopathology, and if any associations with psychopathology are consistent across age, sex, and race. Therefore, specifically studying the base relationship between aberrations in ‘effort valuation’ and psychopathology in general may then provide valuable insight into behavioral impairments spanning several diagnostic categories.

Additionally, sex-specific differences have been observed across multiple forms of psychopathology, especially in disorders that have previously been linked to aberrant reward behavior. These differences include rates of occurrence, type and degree of symptom severity, and treatment response. An example of differing prevalence would be the 2:1 female to male ratio observed in anxiety/depression (Altemus, Sarvaiya, & Neill Epperson, 2014). With respect to symptomatology, previous research in ASD has found that externalizing problems, such as aggressive behavior and hyperactivity, were more prominent in males, whereas internalizing
problems, such as emotional issues in anxiety and depression, were greater in females (Werling & Geschwind, 2013). Our current understanding of the mechanisms behind these differences is limited, and it is still unclear how and to what degree they are influenced by genetics, physiological factors, and societal conditions. Considering that, it is critical to include investigations of sex differences when relating reward behavior to psychopathology. To our knowledge, at the time this research was conducted, no previous research had examined the effects of sex on the relationship between ‘effort valuation’ and any form of psychopathology.

The intent of this RDoC-based study was to take a broad approach to relating reward behavior to psychopathology. To this end, we included the Social Adjustment Inventory for Children and Adolescents (SAICA) and Injury Behavior Checklist (IBC) to also examine the relationship between ‘effort valuation’ and social behavior, aggression, and injurious behavior. Aberrant social behavior and signs of aggression have previously been linked with atypical reward behavior in previous research. For example, in depression, a reduced neural response to social reward has been found among offspring of depressed parents as compared with those whose parents had no history of depression (Olino, Silk, Osterritter, & Forbes, 2015). Similar dysregulated reward mechanisms have been observed in substance use disorders and impulsive-aggressive behavior, and at the time of this study, reward behavior was an understudied component in aggression research (Venables, 2017). These findings indicate that reward behavior could be a key component of many areas of human brain function and investigating atypical reward responses may be important to multiple research domains, including psychopathology.

Against this backdrop, the present study aimed to examine ‘effort valuation’ as a correlate of psychopathology in children and adults, and the moderating effects of sex on the
relationship between ‘effort valuation’ and psychopathology. We hypothesized that ‘effort valuation’ would be a significant correlate of multiple dimensions of psychopathology. If aberrant reward behavior was indeed linked to psychopathology as we predicted, we anticipated that we might also observe sex-related differences in the characterization of that linkage, based on findings from previous research regarding sex differences in mental disorders. As an additional goal, we hoped to further establish the validity of ‘effort valuation’ as a relevant construct for psychiatric research. To achieve that, we aimed to investigate the cross-generational and familial continuity of the construct by comparing measures of ‘effort valuation’ between parents and their children, as well as between siblings. We hypothesized that ‘effort valuation’ would be predictive of similar domains of psychopathology between adults and children and that ‘effort valuation’ would be significantly correlated among siblings and between parents and children.
Materials and Methods

Procedure

Participants were recruited from a variety of sources within the Syracuse, NY and surrounding areas, including the Child and Adolescent Psychiatry Clinic at SUNY Upstate Medical University, child psychiatrists and mental health clinicians working in private practice, and community events (local fairs, festivals, etc.). Children meeting the following criteria were excluded from the study due to their possible confounding influence on results: adopted, sensorimotor disability, a diagnosed neurological condition, a history of head injury with documented loss of consciousness lasting more than 10 minutes, an uncontrolled medical condition, or an inability to understand the English language. For adults, the same exclusion criteria were applied, except adoption. Two additional exclusion criteria were also added to the adult exclusion list: people who did not have the ability to independently complete study tasks, and women who were pregnant or gave birth within 6 months prior to the study visit. At the time of ascertainment, pregnant women were traditionally considered to be part of a ‘vulnerable’ population, with a compromised ability to protect their interests and provide informed consent (Blehar et al., 2013).

An estimate of intelligence quotient (IQ) was obtained from scores on the vocabulary and abstraction subtests of the Shipley-2 (a validated, age-appropriate instrument for subjects between the ages of 7 and 89 years) (Kaya, Delen, & Bulut, 2012). This was applied to both adults and children within the recommended age range. As the mean of these two tests correlates 0.90 with full-scale IQ, subjects with an estimated IQ below 80 were excluded from this study. Informed consent was obtained from all parents and assent was given by all children upon arrival.
for their study visit and the study was approved by the Upstate Medical University Institutional Review Board.

Participants

A total of 1215 children and 1044 parents, with and without a history of psychiatric problems, participated in this study. This study population was drawn from a convenience sample that was purposely enriched for psychopathology via recruitment in local clinics. All children were between the ages of 6 and 12 years (mean age = 9 years, S.D. = 2.2), and their parents were between the ages of 23 and 59 years (mean age = 37 years, S.D. = 7.2). Parental age was capped at 59 years of age to avoid the possibility of cognitive decline, as previous literature has indicated that cognitive decline most commonly occurs starting at 60 years of age (Salthouse, 2010). Although there is a possibility of including participants who are already experiencing cognitive decline by placing our age cap at the edge of cognitive decline onset, given that only 3.1% of adult participants were over 50 years of age, we do not believe that this is a significant enough proportion for our results to be influenced by aging. While there were approximately equal numbers of female and male children (49% v. 51%), significantly more of the participating parents were female than male (69% v. 31%). Participants were diverse in their racial backgrounds, with 65% of parents identifying as White, 24% Black, and 11% other or multiple races, and 55% of children identifying as White, 25% Black, and 20% other or multiple races. Additionally, 7% of parents and 11% of children were Hispanic. Parents reported both for themselves and for their children whether they had ever sought mental health care for emotional or behavioral problems, with 41% of children and 45% of parents reporting such psychiatric history. The dataset included a total of 770 different families, with an average family size of 2.93. Since 25% of participants chose not to report their household income, multiple imputation
was utilized to handle missing adult income data. Ten iterations of imputation were conducted. Demographic information including education, employment, marital status, age, IQ, ancestry, and sex were used to predict income in the imputation procedure. When modeled together, these variables explained a large proportion of the variance in income ($R^2 = 0.698$). Detailed demographic information is available in Appendix Chapter 2 Supplementary Table 2.1.

Measures

Study visits were approximately 3 hours in length and involved the completion of a variety of computerized inventories and behavioral paradigms.

Effort Expenditure for Rewards Task: Reward Sensitivity and Motivation

The Effort Expenditure for Rewards Task (EEfRT) was developed by Treadway and colleagues to measure effort-based decision-making (Treadway et al., 2009). The EEfRT consists of a multi-trial game in which participants attempt to maximize their monetary rewards. The rules of the game were explained to each subject as follows: 1) They were instructed to choose between two types of tasks for each trial (‘Easy Task’ or ‘Hard Task’), where the ‘Hard Task’ provided the opportunity for much greater monetary gain relative to the ‘Easy Task’; 2) The ‘Easy Task’ required 30 button presses with the dominant index finger within 7 seconds for a fixed reward value of $1.00; 3) The ‘Hard Task’ required 100 button presses with the non-dominant fifth finger within 21 seconds for a varying assigned reward value between $1.24 and $4.30; 4) Subjects were expected to complete multiple trials and were given a 20-minute time limit to complete as many trials as they could; 5) For the adult trials, three levels of probability were presented for obtaining a reward upon successful trial completion: ‘high’ (88%), ‘medium’ (50%), and ‘low’ (12%). This means that some adult trials did not result in a reward, even if the
subject successfully completed the task. According to Treadway and colleagues, this probability component is designed to add complexity to the decision-making aspect of selecting the task difficulty, to ensure that neither a strategy of choosing only the easy or hard options would lead to ‘optimal’ performance. With this safeguard in place, subjects’ decisions better reflect individual differences in willingness to expend ‘effort’ for a given level of reward. However, since this component required the subjects to have a complete understanding of the concept of probability and its effect on the reward outcome to properly impact the decision-making process, it was not practical to apply to child participants given their young age. As a result, the probability component is not present in the child version of the EEfRT task. All subjects received trials presented in the same randomized order. If participants did not choose between the hard or easy task, the trial was marked as a ‘time-out’ and was not included in the calculation of summary variables.

Our outcome variables for the EEfRT task were hard-task choice percentage and reward sensitivity. The hard-task choice percentage was calculated as the percentage of trials for which that participant chose the hard task. Individuals who chose the hard task more than 50% of the time were considered to have high hard-task choice percentage, and those who chose the hard task less than 50% of the time were considered to have low hard-task choice percentage. To derive reward sensitivity, a logistic beta weight was calculated on a per-participant basis via logistic regression with an individual’s hard task choice as the outcome (dependent) variable and reward magnitude (monetary amount; dollars) as the predictor (independent) variable. Therefore, the reward sensitivity variable is a measure of the degree to which the reward amount influences an individual’s choice between hard and easy tasks.
**Adult Self Report: Dimensional Measures of Psychopathology**

The Adult Self Report (ASR) was used to measure psychopathology in adult participants. This 126-item self-report measure is well validated and widely used in clinical practice and research to assess symptoms of psychopathology and adaptive functioning in individuals aged 18-59 years (Rescorla & Achenbach, 2004). Participants were asked to respond to each item on a three-point scale: from *not true, often true, or very true*, within the past 3 months. The ASR provides T-scores for seven syndrome scales (anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behavior, and rule-breaking behavior), six scales specific to symptoms of DSM diagnoses (affective disorders, anxiety disorders, somatic problems, avoidant personality features, attention-deficit/hyperactivity problems, and antisocial personality features), three composite scores (internalizing composite, externalizing composite, and total problems composite), and four scales assessing substance use (tobacco, alcohol, recreational drugs, and substance use composite). Due to the nature of the ASR assessment, the minimum possible T-score generated is 50, which would represent a participant whose level of self-reported psychopathology is that of a typically developing, psychiatrically unaffected individual (no psychopathology). A T-score of 50 then represented a ‘zero-value’ in our study.

**Child Behavior Checklist: Dimensional Measures of Psychopathology**

The Child Behavior Checklist (CBCL) was used to measure psychopathology in children. This 113-item parent-report measure is well validated and widely used in clinical practice and research to assess emotional and behavioral functioning in children ages 6-18 years (Achenbach, 1991). Parents were asked to respond to each item on a three-point scale: from *not true, often true, or very true*, which indicated how true the item is for their child within the past 3 months.
The CBCL provides T-scores for eight syndrome scales (anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior), nine DSM-oriented scales (affective problems, anxiety problems, somatic problems, attention-deficit/hyperactivity problems, oppositional defiant problems, conduct problems, sluggish cognitive tempo, obsessive compulsive problems, and post-traumatic stress problems), and three composite scores (internalizing composite, externalizing composite, and total problems composite). The CBCL shares the same minimum T-score as the ASR (50), so our outcome variables follow the same logic described in the section above.

**Social Adjustment Inventory for Children and Adolescents: Dimensional Measures of Functioning**

The Social Adjustment Inventory for Children and Adolescents (SAICA) was used to measure children’s functioning across several domains. This 78-item semi-structured interview was designed to assess social functioning in children ages 6 to 18 years (John, Gammon, Prusoff, & Warner, 1987). Direct responses to the interview questions from the children were recorded on a four-point scale, with higher scores indicating greater impairment. Mean scores were created for four domains of functioning: current school functioning, spare time activities, peer functioning, and current home behavior. An overall functioning score was calculated by taking the mean of these subscale scores.

**Injury Behavior Checklist: Dimensional Measures of Psychopathology**

The Injury Behavior Checklist (IBC) was used to measure dangerous and problem behavior in children. This 24-item parent-report measure asks respondents to rate the frequency
of injurious behaviors displayed by their child (Potts et al., 1997). For each item, parents were asked to rate their children on a five-point scale from *not at all* to *more than once a week*. Items were sum-scored, with possible scores ranging from 24 to 120, and with higher scores indicating more frequent injurious and problem behaviors.

*Statistical Analyses*

Statistical analyses used R version 3.4.1. A series of negative binomial regression models examined ‘effort valuation’ as a predictor of psychopathology in children. Negative binomial regression was used to account for non-normal distribution of the outcome variables, which were T-scores. These variables also had an over-representation of zeros because both the ASR and CBCL T-scores less than the mean (zero) are fixed at zero by the developers of the ASR and CBCL scoring algorithms. These extra zeros were modeled as zero inflation within the negative binomial framework. Main effects of hard-task choice percentage, reward sensitivity, and sex were tested, as well as interaction effects of hard-task choice percentage, reward sensitivity, and sex. All child models covaried for parent income and education, but not age, as there was no association between child's age and EEfRT scores.

Like with the children, negative binomial regression was used to account for non-normal distribution of outcome variables in parents. Main effects of hard-task choice percentage, reward sensitivity, and sex were tested, as well as interaction effects of hard-task choice percentage, reward sensitivity, and sex. All adult models covaried for demographic variables including age, IQ, education, employment, income, race, and marital status.

Robust standard errors were used across all models to account for non-independence in the data such as those caused by familial relationships. Paired-sample correlation tests using
intraclass correlations as well as Kendall's tau were also conducted to determine the degree of sibling-sibling and parent-child correlations.

The Benjamini Hochberg False Discovery Rate method (Benjamini & Hochberg, 1995) corrected for multiple testing. This procedure is a recommended alternative to Bonferroni-type corrections, which are often criticized for increasing the likelihood of type-II errors, particularly when a large number of tests are conducted (Perneger, 1998). A 5% false discovery rate was utilized for determining the significance of findings across both groups. The total number of tests conducted was 18 for the adults and 21 for the children. P-values reported in the results are FDR-adjusted.
Results

Appendix Chapter 2 Supplementary Tables 2.2 and 2.3 include bivariate correlations between measures of hard-task choice percentage, reward sensitivity, and each of the outcome variables tested.

EEfRT Task Statistics

Prior to administration of the EEfRT, adult participants were given a short questionnaire assessing their understanding of basic probability. Participants who did not demonstrate adequate understanding of probability were not allowed to participate in the EEfRT. For the adult participant population, average proportion of hard task choices was 36.76%, and the average reward sensitivity betaweight was 0.765. Mean percent completion rate among adults was 93.47%. On average, adult participants timed out in their choice of the hard versus easy task in 5.90% of trials. For the child participant population, average proportion of hard task choices was 58.34%, and the average reward sensitivity betaweight was 0.118. Mean percent completion rate among children was 87.27%. On average, child participants timed out in their choice of the hard versus easy task in 1.38% of trials. Additionally, we calculated the number of participants in each population who chose only easy or only hard tasks (possibly indicating lack of task comprehension), to confirm that these subjects’ choices did not drive the reported associations with psychopathology. For adults, 0.7% of participants chose only easy tasks, and 0.0% of participants chose only hard tasks. For children, 0.6% of participants chose only easy tasks, and 3.5% of participants chose only hard tasks.

Models predicting child psychopathology

Additional interactions between reward sensitivity and sex were observed in the models predicting DSM-5 anxiety problems. At low reward sensitivity, increased anxiety problems were
observed for male subjects relative to female subjects ($\beta = 0.522$, $p = 0.041$) (Figure 2.1).

Similarly, we found increased thought problems at low reward sensitivity for male subjects in comparison to female subjects ($\beta = 0.438$, $p = 0.045$) (Figure 2.2).

**Figure 2.1.** Reward sensitivity and sex in CBCL DSM anxiety problems
A main effect of hard-task choice percentage was observed in the models predicting ASR Alcohol Use. At high hard task choice percentage, increased alcohol usage was observed for our subjects ($\beta = 0.531, p = 0.0083$) as compared to those with low hard task percentage (Figure 2.3). Additionally, a main effect of hard-task choice percentage was observed in the models predicting ASR Drug Use. At high hard task choice percentage, increased drug usage was observed for our subjects ($\beta = 3.398, p = 0.014$) as compared to those with low hard task choice percentage (Figure 2.4).
Figure 2.3. Effort hard-task choice percentage in ASR alcohol use.

Figure 2.4. Effort hard-task choice percentage in ASR drug use.
Familial Transmission

In examining the transmission of ‘effort valuation’ within families, we found significant sibling-sibling correlations but no significant parent-child correlations. When examining associations of ‘effort valuation’ between siblings using EEfRT hard task choice percentage, we found a significant positive correlation between both full siblings ($r = 0.13, p = 0.039$) and half siblings ($r = 0.19, p = 0.008$). However, in examining associations of ‘effort valuation’ between these children and their parents using EEfRT hard task choice percentage, we found no significant correlations between children and their respective mothers and fathers ($p >> 0.05$).
Discussion

The present study sought to test hypotheses regarding the relationship between ‘effort valuation’ and psychopathology in children and adults, and to determine the impact of sex on these relationships. As we hypothesized, ‘effort valuation’ was a significant predictor of multiple dimensions of psychopathology, some of which were moderated by sex. However, our hypothesis that ‘effort valuation’ would be linked to the same psychopathologies between adults and children was not supported. Additionally, while we found significant relationships between ‘effort valuation’ and several areas of psychopathology and functioning that varied by sex, many of our tests of association were negative and correlations between ‘effort valuation’ and psychopathological outcomes were generally small. Given the large size of our sample, these negative findings cannot be attributed to low statistical power. These results suggest that dysfunction in ‘effort valuation’ may be a contributing factor rather than a driving force for a range of psychopathology and impairment in children and adults.

Contrary to our hypothesis, ‘effort valuation’ was associated with different psychopathologies for adults and children. Additionally, while a positive sibling-sibling correlation was found for ‘effort valuation’, no significant correlation was found between parents and their children. Given that many psychiatric conditions are transmitted in families, the lack of parent-child correlations for ‘effort valuation’ presents important questions to consider for future research, especially since there have been no prior familial studies of ‘effort valuation’ in psychopathology to date. This result may mean that the child and adult assessments for ‘effort valuation’ do not gauge the same constructs. For example, the parent version of the EEfRT included an additional reward evaluation component (probability of trial actually resulting in reward) in each trial which was not present in the child version. That difference may have
impacted adult subjects’ decision-making process. Alternatively, the lack of parent-child correlation could indicate that ‘effort valuation’, and its correlates, change as a child moves through the stages of development. At the time of assessment, children were between the ages of 6-12. Changes in ‘effort valuation’ have been previously observed in a comparison study between 4 and 6-year old children where the older children displayed greater ability to evaluate effort and reward quality (Benozio & Diesendruck, 2015).

Previous studies in children have found sex and reward sensitivity to be linked to anxiety disorder, such that clinically anxious male youth displayed both decreased risk taking and sensitivity to reward in comparison to clinically anxious females, as well as typically developing male and female youths (Dorfman, Rosen, Pine, & Ernst, 2016). Our results provide further support for the relationship between sex, reward sensitivity, and anxiety disorder, where at low reward sensitivity we found that male children reported greater anxiety problems than female children. It has become increasingly apparent that the study of gender differences in adolescent anxiety is important, given that anxiety disorders often begin to present symptomatically in adolescence. A longitudinal study of adolescents demonstrated a greater level of functional impairments among anxious males than anxious females with regards to academic performance, self-esteem, sense of well-being, and socialization with friends (Derdikman-Eiron et al., 2012).

As a result, the gender-specific alterations in the reward system measures observed both here and in previous research suggest that it is possible that treatments for anxiety that target the reward system may need to be tailored to gender. However, further research that specifically assesses this is necessary to make a definitive determination.

While past studies have also found relationships between autism spectrum disorders (ASDs) and both aberrant ‘effort valuation’ and diminished reward processing in children...
(Mosner et al., 2017; Scott-Van Zeeland, Dapretto, Ghahremani, Poldrack, & Bookheimer, 2010), we found that this relationship may differ based on sex. Our results revealed that lesser reward sensitivity was associated with a higher degree of thought problems in male children versus females. Thought problems according to the CBCL scale include seeing or hearing things, repeating acts, and strange ideas/behavior. In children, thought problems have been linked with relatively high sensitivity and specificity to ASD (Mazefsky, Anderson, Conner, & Minshew, 2011). To our knowledge, no previous studies have specifically examined the moderating effects of sex in relating hard-task choice percentage or reward sensitivity with ASD in children. However, with ASD being a predominantly male disorder (Loomes, Hull, & Mandy, 2017), understanding gender-specific alterations in reward behavior may be important for future research as well as future treatment development.

Limitations/Future Directions

The present work has several limitations. The use of self-reported race, rather than genetic data, to understand ancestry may have placed greater weight on the social over the biological component of an individual's ancestral background. Participants' self-reported racial identity may not fully align with their genetic ancestry, instead representing their personal understanding of their ancestral background. For example, Hispanic participants may only identify with their Hispanic ethnicity rather than any racial category. Future research should compare the implications of self-identified ancestry versus genetic ancestry to determine if these differing ways of defining one's heritage diverge in relation to ‘effort valuation’ and associated psychopathological outcomes.

In the present study, we were unable to examine the impact of racial identities other than White/Caucasian and Black/African American due to the low number of individuals who
identified with other races. Also, our adult sample was disproportionately female, so future studies should seek to recruit a more balanced sample in addition to correcting the under-representation of other racial minorities besides Black/African American. Few participants displayed elevated symptoms for some of the psychological problems examined in this study, so future research collecting data from more individuals who experience particular psychological problems may reveal new or clearer patterns between ‘effort valuation’ and specific forms of psychopathology.

With regards to our assessments of psychopathology, we acknowledge that our usage of parent-reports as measures for both child and parent psychopathology is an important limitation as it represents an indirect rather than direct measure of child psychopathology. While the Child Behavior Checklist and Adult Self Reports cover a wide range of psychopathological outcomes, further research on ‘effort valuation’ should be conducted in the context of additional psychopathologies not specifically included in the CBCL or ASR, such as schizophrenia or autism spectrum disorder. Relationships with those two disorders in particular have been established in adults using the EEfRT paradigm (Barch, Treadway, & Schoen, 2014; Damiano et al., 2012; McCarthy et al., 2016; Treadway et al., 2015), but studies of children have not been conducted to date.

In addition, future studies should explore the relationship between other Positive Valence System constructs and psychopathology and impairment using a similar approach, to determine if these constructs differentially associate with various forms of psychopathology and functioning. It will be important to consider longitudinal work to investigate the stability of ‘effort valuation’ over time, especially with regards to children passing through stages of their
development. Such work will be key to understanding how ‘effort valuation’ at various stages of life might be used to predict future psychopathology and functioning in individuals.

Conclusions

The present study establishes ‘effort valuation’ as a relevant psychological construct for understanding psychopathology and functioning in adults and, especially, in children. Findings from this study both confirm and expand upon the current state of knowledge in the field with regards to examining sex when considering how ‘effort valuation’ relates to anxiety disorder and autism spectrum disorders in children, and alcohol and drug use in adults. The associations observed with regards low hard-task choice percentage, low reward sensitivity, and these types of psychopathologies indicate that deficits in reward processing behavior may be an important therapeutic target. Furthermore, hard-task choice percentage and reward sensitivity may be potentially modifiable risk factors, and our data demonstrates that the degree to which these risk factors impact pathology might be a key factor in developing targeted treatment strategies, as well as an important consideration in further research to understand the biological mechanisms underlying these behavioral deviations. These results highlight the importance of examining ‘effort valuation’ as it relates to areas of psychopathology and functioning not previously examined and provides evidence in favor of longitudinal study of ‘effort valuation’ to further determine the stability of the construct over time and through developmental stages.
### Appendix Chapter 2

**Supplementary Table 2.1. Participant Demographics**

<table>
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<th>Demographics</th>
<th>Percentage</th>
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<td>Sex (% female)</td>
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<tr>
<td>(% two or more races)</td>
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</tr>
<tr>
<td>(% other)</td>
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</tr>
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### Supplementary Table 2.2. Effort Hard Task Choice Bivariate Correlations

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**Supplementary Table 2.3.** Reward Sensitivity Bivariate Correlations

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Bibliography Chapter 2


Chapter 3: Study Two – Empirical Validation of Effort Measures in Children and Adults: Divergent Validity, Familial Similarity, and Predictive Validity for Psychopathology

Introduction

The previous chapter discussed the initial foray into conducting an RDoC-based approach to research examining the relationship between reward behavior and psychopathology. Findings from that study established that the ‘effort’ component of reward behavior was indeed a relevant psychological construct for understanding psychopathology and function in both adults and children. Additionally, the previous study represented the first published application of the EEfRT task in children. The focus of this next study was multifold: to further advance the groundwork laid by the initial study by replicating the analyses in a larger population to determine whether the same psychopathological associations would present, further investigate the apparent lack of familiality among measures of ‘effort’, and empirically validate ‘effort’ as distinct from other constructs/subconstructs within the PVS domain. In particular, analytical models were restructured to align more closely with an RDoC approach compared to those in Study 1, with the removal of models using the SAICA, IBC, and DSM-specific scales from the ASR/CBCL. Because this original study was the first application of an RDoC-based approach to reward behavior research, we felt that it was essential to continue our research in such a way to also evaluate the scientific rigor of the initial findings before proceeding further to other modalities of investigation. This also served to bolster the robustness of our findings in contributing to future revisions of the RDoC research framework, one of the overarching goals of our research.
As discussed previously, reward processing encompasses human behavioral and neurobiological responses to positive motivational situations, and alterations in this processing is a known feature of multiple forms of psychopathology (Zald & Treadway, 2017). Given that symptoms of altered reward processing are specifically referred to as diagnostic criteria for multiple psychiatric disorders in the DSM-V, the study of reward processing is a key component to understanding human psychopathology (American Psychiatric Association, 2013). Reward processing can be broken down further into components such as reward responsiveness, reward learning, and reward valuation, each of which may be related to and impacted to different degrees in particular psychiatric disorders (T. Insel et al., 2010). Reward valuation, as an example, typically refers to the processes by which the probability and benefits of a prospective outcome are computed by reference to external information, social context, and/or prior experience. Within this reward valuation component are further sub-elements that have been studied via multiple varying approaches. The ‘reward’ sub-construct specifically refers to perception of the magnitude, valence, and predictability of the prospective outcome. The ‘delay’ sub-element refers to the perception of the expected time interval prior to attainment of the prospective outcome. Each of these elements has been examined from both a neurobiological perspective, via the measured activity of dopaminergic neurons or through neuroimaging, and a behavioral perspective, via task-based experiments or self-reports (Klein-Flügge, Kennerley, Saraiva, Penny, & Bestmann, 2015; Kobayashi & Schultz, 2008; Schultz, Carelli, & Wightman, 2015). The focus of the current study is the less-studied third sub-element of reward valuation: ‘effort’. The ‘effort’ sub-element refers to perception of the value of the prospective outcome as a function of its magnitude and the perceived costs of the physical or cognitive labor required to obtain it (NIMH, 2016). Our chosen method for assessing ‘effort’ is the Effort Expenditure for
Rewards Task (EEfRT), an NIMH-endorsed behavioral task that has been used previously to study ‘effort’ in adults with anhedonia, major depressive disorder, and schizophrenia (MDD) (Barch et al., 2014; NIMH, 2016; Treadway et al., 2012, 2009).

Previous research relating ‘effort’ and/or motivation with psychopathology has consistently found significant differences in effort-based decision-making between persons with psychiatric disorders and healthy comparison subjects. Prominent disorders featuring effort-related motivational dysfunction include MDD, autism spectrum disorder (ASD), and schizophrenia. The components of reward behavior that are affected range from decreased sensitivity to reward parameters in ASD, to decreased overall ‘effort’ expenditure in MDD, to inefficient ‘effort’ allocation in ASD, MDD, and schizophrenia (Damiano et al., 2012; McCarthy et al., 2016; Mosner et al., 2017; Treadway et al., 2012, 2015). In MDD in particular, decreased motivation is a key symptom most strongly correlated with negative impacts on social functioning and employment-related factors such as days in bed, days of lost work, and low work productivity (Salamone, Yohn, López-Cruz, San Miguel, & Correa, 2016; Stahl, 2002; Tylee, Gastpar, Lépine, & Mendlewicz, 1999). Research on schizophrenia and ‘effort’ found that individuals with schizophrenia demonstrated fundamental problems with engaging in effortful behavior that was independent of difficulties with experiencing pleasure or setting pleasure-based goals, and that individuals with schizophrenia showed reduced selection of high-effort alternatives on a novel decision-making task (Gard et al., 2014; Gold et al., 2013b).

Two other disorders with links to abnormal reward behavior are attention-deficit/hyperactivity disorder (ADHD) (Marx, Hacker, Yu, Cortese, & Sonuga-Barke, 2018) and substance use disorders (SUDs) (García-García et al., 2014). People with these disorders are more likely than unaffected individuals to find it difficult to optimally process immediate versus delayed rewards.
during decision-making, opting for immediate rewards over much larger/more valuable delayed rewards. Current research seeks to determine the neurobiological roots of this behavior by studying elements known to be involved in the reward system at the molecular level (adenosine, dopamine, and GABA), and at the brain circuitry level (ventral tegmental area and nucleus accumbens). While this research is ongoing, it is already clear that aberrant reward processing is a central component to the impulsivity that characterizes these disorders (Rosch, Mostofsky, & Nebel, 2018). Collectively, this work has demonstrated the wide variety of psychiatric disorders in which ‘effort’-related reward behavior is affected. Therefore, assessing ‘effort’ in a broader context rather than on a disorder-specific basis may be valuable in understanding the core impairments that are common across psychopathologies.

Many of the disorders previously linked to dysfunctional reward behavior also show skewed sex ratios in prevalence; e.g., ADHD shows a 3:1 male:female ratio, while anxiety and depression are two times more common in females (Staller & Faraone, 2006). Regarding symptoms, previous research found that externalizing problems, such as aggressive behavior and hyperactivity, were more prominent in males with ASD, whereas internalizing problems, such as emotional issues, have greater prevalence in females with anxiety and depression (Dorfman et al., 2016; Werling & Geschwind, 2013). Different patterns have also been found between men and women for determinants of functional disability in MDD, as well as notable sex differences in clinical features, cognitive impairment, and their respective associations among schizophrenia patients (Carmona et al., 2018; Mu et al., 2020). Since research has been conducted thus far into sex-specific symptom differences within various psychiatric disorders, and ‘effort’ impairment has been identified as a common feature of psychopathology, it follows that investigation into the possible sex-differences in ‘effort’ behavior may be important to delineate. A recent study of
sex differences in psychopathology among children aged nine and ten revealed that males had higher scores and greater frequency of clinically meaningful levels of psychopathology than females did (Loso et al., 2021). It is therefore highly relevant to study domains of function, such as reward, that are impacted by psychopathology as early as childhood, and to determine how this effect differs among males versus females.

Familiality is another key dimension of reward behavior whose evaluation may provide important context for its association with psychopathology. Many psychiatric disorders have been identified as familial or as having familial risk factors, including each of the disorders mentioned above (Díaz-Castro, Hoffman, Cabello-Rangel, Arredondo, & Herrera-Estrella, 2021; Grant & Chamberlain, 2020; Thapar, Cooper, Eyre, & Langley, 2013; Xie et al., 2019; Zalar, Blatnik, Maver, Klemenc-Ketiš, & Peterlin, 2018). Assessing the familiality of measures of impairment in ‘effort’ and/or reward processing is important to understanding what degree of risk these aberrations pose towards the development of psychopathology. One study used a biomarker of reward sensitivity (frontal EEG asymmetry) along with family history of MDD and/or panic disorder (PD) to determine if an association between biomarker and risk factor existed independent of DSM-IV diagnosis. This study found that frontal EEG asymmetry was associated with a family history of MDD even after controlling for DSM-IV diagnosis, indicating that reduced sensitivity to reward indexed risk for depression over and above the variance explained by the diagnosis (Nelson et al., 2013). Considering this, research on associations between psychopathology and impairments in ‘effort’ in a family-based context may be particularly useful, as familiality can be analyzed via direct comparison of measures between parents and their children.
The present study sought to empirically validate ‘effort’ as a construct of human reward processing via multiple different behavioral tasks and self-report measures of psychopathology. To our knowledge, this study would be the first to attempt this validation in a population that included children. We hypothesized that the ‘effort’ construct would show divergent validity from other constructs of reward behavior in children as well as adults. Additionally, we assessed sex differences in the relationship between ‘effort’ and psychopathology in both adults and children to determine whether these differences would show patterns similar to common findings in the literature regarding sex-specificity in psychopathologies. Because many psychiatric disorders feature impaired ‘effort’ behavior and are familial, we hypothesized that measures of ‘effort’ would also correlate within families. We also hypothesized that, in both adults and children, measures of ‘effort’ would be associated with self-report scales related to psychopathology that had previously been linked to abnormal reward behavior, but not scales associated with other forms of psychopathology. In particular, we expected that ‘effort’ would show its strongest association with measures linked to ADHD, ASD, schizophrenia, depression, and anxiety across both children and adults.
Materials and Methods

Note: Given that this Study 2 uses an expanded participant sample from Study 1, some of the following sections reuse descriptions from the ‘Materials and Methods’ section in Chapter 2. They have been repeated for the convenience of the reader as they are still components of the analyses of Study 2. Sections with no consequential changes relative to their Chapter 2 counterparts have been marked with an asterisk (*) for transparency.

Procedure*

Participants were recruited from a variety of sources within the Syracuse, NY and surrounding areas, including the Child and Adolescent Psychiatry Clinic at SUNY Upstate Medical University, child psychiatrists and mental health clinicians working in private practice, and community events (local fairs, festivals, etc.). Children meeting the following criteria were excluded from the study due to their possible confounding influence on results: adopted, sensorimotor disability, a diagnosed neurological condition, a history of head injury with documented loss of consciousness lasting more than 10 minutes, an uncontrolled medical condition, use of psychotropic medications, or an inability to understand the English language.

For adults, the same exclusion criteria were applied, except adoption. Two additional exclusion criteria were also added to the adult exclusion list: people who did not have the ability to independently complete study tasks, and women who were pregnant or gave birth within 6 months prior to the study visit. At the time of ascertainment, pregnant women were traditionally considered to be part of a ‘vulnerable’ population, with a compromised ability to protect their interests and provide informed consent (Blehar et al., 2013). An estimate of intelligence quotient (IQ) was obtained from scores on the vocabulary and abstraction subtests of the Shipley-2 (a validated, age-appropriate instrument for subjects between the ages of 7 and 89 years). This was
applied to both adults and children within the recommended age range. As the mean of these two tests correlates 0.90 with full-scale IQ, subjects with an estimated IQ below 80 were excluded from this study. Informed consent was obtained from all parents and assent was given by all children upon arrival for their study visit and the study was approved by the Upstate Medical University Institutional Review Board.

Participants

A total of 2806 participants (1536 children and 1270 parents) took part in this study. The study required parents to report both for themselves and for their children whether they had ever sought mental health care for emotional or behavioral problems, and it was reported that 52% of children and 52% of parents had such psychiatric history. Our study population was drawn from a convenience sample that was purposely enriched for psychopathology via recruitment in local clinics to ensure a broad range of psychopathology into both the clinical and normal ends of the distribution. Psychiatric participants were not selected based on any particular form of psychopathology, as our study was designed to employ an agnostic ascertainment scheme. All children were between the ages of 6 and 12 years (mean age = 9, S.D. = 3.1), and their parents were between the ages of 23 and 59 years (mean age = 37, S.D. = 6.9). Parental age was capped at 59 years of age to avoid the possibility of age-related cognitive decline, as previous literature has indicated that cognitive decline most commonly occurs starting at 60 years of age (Salthouse, 2010). Although there is a possibility of including participants who are already experiencing cognitive decline by placing our age cap at the edge of cognitive decline onset, given that only 3.1% of adult participants were over 50 years of age, we do not believe that this is a significant enough proportion for our results to be influenced by aging. While there were approximately equal numbers of female and male children (49% vs. 51%), significantly more of the
participating parents were female than male (69% vs. 31%). Participants were diverse in race, with 65% of parents identifying as White, 24% Black, and 11% other or multiple races, and 55% of children identifying as White, 25% Black, and 20% other or multiple races. Additionally, 6% of parents and 11% of children were Hispanic. The dataset includes 1215 different families, with an average size of 2.94. Since 25% of participants chose not to report their household income, multiple imputation was utilized to handle missing adult income data. In total, ten iterations of imputation were conducted. IQ and demographic information including self-reported levels of education, employment, marital status, age, race, and sex were used to predict income in the imputation procedure. When modeled together, these variables explained a large proportion of the variance in income ($R^2 = 0.698$), which was consistent with the variance observed in the discovery sample. Since missing data was not a problem for the other demographic variables (education, employment, age, marital status, IQ, race, and sex), multiple imputation for those variables was not necessary and was not performed. Detailed demographic information is available in in Appendix Chapter 3 Supplementary Table 3.1.

Measures

Study visits were approximately 3 hours in length and involved the completion of a variety of computerized inventories and behavioral paradigms.

Effort Expenditure for Rewards Task*

The Effort Expenditure for Rewards Task (EEfRT) was developed by Treadway and colleagues to measure effort-based decision-making (Treadway et al., 2009). The EEfRT consisted of a multi-trial game in which participants attempt to maximize their monetary rewards. The rules of the game were explained to each subject as follows: 1) They were instructed to choose between two types of tasks for each trial: ‘Easy Task’ or ‘Hard Task’, where
the ‘Hard Task’ provided the opportunity for much greater monetary gain relative to the ‘Easy Task’; 2) The ‘Easy Task’ required 30 button presses with the dominant index finger within 7 seconds with a fixed reward value of $1.00; 3) The ‘Hard Task’ required 100 button presses with the non-dominant fifth finger within 21 seconds with a varying assigned reward value between $1.24 and $4.30; 4) Subjects were expected to complete multiple trials and were given a 20 minute time limit to complete as many trials as they could; 5) For the adult trials, three levels of probability were presented for obtaining a reward upon successful trial completion: ‘high’ (88%), ‘medium’ (50%), and ‘low’ (12%). This means that some adult trials did not result in a reward, even if the subject successfully completed the task, to ensure that participants could not default to choosing only easy or hard options to optimize their performance (Treadway et al., 2009). Because this component requires an understanding of probability, this was not applied in the child trials. If participants did not choose between the hard or easy task, the trial was marked as a ‘time-out’ and was not included in the calculation of summary variables.

All subjects received trials presented in the same randomized order. At the beginning of each trial, in the adult version of the EEfRT task only, subjects are provided with one of the three winning probability levels (88%, 50%, or 12%), which applied equally regardless of whether the hard or easy task was picked. This probability component is designed to add complexity to the decision-making aspect of selecting the task difficulty, to ensure that neither a strategy of choosing only the easy or hard options would lead to ‘optimal’ performance. With this safeguard in place, subjects’ decisions better reflect individual differences in willingness to expend ‘effort’ for a given level of reward (Treadway et al., 2009). However, since this component required the subjects to have a complete understanding of the concept of probability and its effect on the reward outcome to properly impact the decision-making process, it was not practical to apply to
child participants given their young age. As a result, the probability component is not present in the child version of the EEfRT task.

Our outcome variables for the EEfRT task were hard-task choice percentage and reward sensitivity. The hard-task choice percentage was calculated as the percentage of trials for which that participant chose the hard task. We categorized individuals as having relatively “high” or “low” hard-task choice percentage based on a median split of hard task choice percentage. To derive reward sensitivity, a logistic beta weight was calculated on a per-participant basis via logistic regression with an individual’s hard task choice as the outcome (dependent) variable and reward magnitude (monetary amount; dollars) as the predictor (independent) variable. Therefore, the reward sensitivity variable is a measure of the degree to which the reward amount influences an individual’s choice between hard and easy tasks.

Adult Self Report*

The Adult Self Report (ASR) was used to measure psychopathology in adult participants. This 126-item self-report measure is well validated and widely used in clinical practice and research to assess symptoms of psychopathology and adaptive functioning in individuals aged 18-59 years (Rescorla & Achenbach, 2004). Participants were asked to respond to each item on a three-point scale: from not true, often true, or very true, within the past 3 months. The ASR provides T-scores for seven syndrome scales (anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behavior, and rule-breaking behavior), three composite scores (internalizing composite, externalizing composite, and total problems composite), and four scales assessing substance use (tobacco, alcohol, recreational drugs, and substance use composite). The ASR also provides T-scores for six scales specific to symptoms of DSM diagnoses, but we elected not to use these scales in analyses to align with the
RDoC approach more closely. Due to the nature of the ASR assessment, the minimum possible T-score generated is 50, which would represent a participant whose level of self-reported psychopathology is that of a typically developing, psychiatrically unaffected individual (no psychopathology). A T-score of 50 then represented a ‘zero-value’ in our study. More detailed information is available in Appendix Chapter 3 Supplementary Table 3.2.

*Child Behavior Checklist*

The Child Behavior Checklist (CBCL) was used to measure psychopathology in children. This 113-item parent-report measure is well validated and widely used in clinical practice and research to assess emotional and behavioral functioning in children ages 6-18 years (Achenbach, 1991). Parents were asked to respond to each item on a three-point scale: from *not true*, *often true*, or *very true*, which indicated how true the item is for their child within the past 3 months. The CBCL provides T-scores for eight syndrome scales (anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior), and three composite scores (internalizing composite, externalizing composite, and total problems composite). The CBCL also provides T-scores for nine DSM-oriented scales, but we elected not to use these scales in analyses to align with the RDoC approach more closely. The CBCL shares the same minimum T-score as the ASR (50), so our outcome variables follow the same logic described in the section above. More detailed information is available in Appendix Chapter 3 Supplementary Table 3.2.

*Additional Behavioral Measures*

The Delay Discounting Task (DDT) and Probability Discounting Task (PDT) assess choice behaviors in the form of preferences and thresholds for selecting instantaneous versus
delayed rewards. Briefly, in a series of delay trials, subjects choose between receiving a large reward ($10) after a delay (1-365 days) or a smaller amount (e.g., $2) immediately or a probabilistic amount (e.g., with a 25% chance). For each delay, the immediate reward amount is changed based on previous responses until an indifference value is reached. The indifference value is defined as the smallest amount of money chosen for immediate receipt instead of waiting the specified delay in order to receive the maximum (Richards, Zhang, Mitchell, & de Wit, 1999). Values used in the analysis and results refer to the area under the curve (AUC) from the indifference point plots from the delay discounting and probability discounting tasks. The DDT is an NIMH-endorsed method for the study of the ‘delay’ subconstruct of Reward Valuation (National Institute of Mental Health, 2018).

The Iowa Gambling Task (IGT) has been extensively used to probe expectancy and reward prediction error in both adults and children. Briefly, participants are presented with four options (decks of cards for adults, pirate chests for children), each of which contains cards that reward or punish the player by adding or subtracting money from their account. Two of the options led to net increases over the course of repeated play (advantageous options) while the other two lead to net decreases (disadvantageous options). The player is instructed to maximize winnings, which requires learning to determine which options will lead to long-term gains and which to long-term losses. The net difference between the number of draws from advantageous versus disadvantageous options over time indexes performance, and the latency value indexes the time taken for an individual to learn the characteristics of each option (Bechara, Tranel, & Damasio, 2000; Cauffman et al., 2010; Garon & Moore, 2004). The IGT is an NIMH-endorsed method for the study of Reward Learning (National Institute of Mental Health, 2018).
The Temporal Experience of Pleasure Scale (TEPS) is a validated, self-administered, 18-item questionnaire that measures anticipatory and consummatory experiences of pleasure in adults. The instrument is divided into a ten-item assessment of anticipatory experiences of pleasure and an eight-item assessment of consummatory experiences of pleasure. The response format is a six-point Likert scale, with possible responses ranging from (1) very false for me to (6) very true for me. The analogous Pleasure Scale for Children (PSC) is a validated, self-administered, 39-item questionnaire that measures expectance and reward in school-age children. The instrument was created to assess anhedonia in children. Subjects rate their anticipated level of ‘happiness’ on the occurrence of 39 different events and activities on a three-point Likert scale with possible responses including: (1) wouldn’t matter; (2) happy; (3) very happy (Gard, Gard, Kring, & John, 2006; KAZDIN, 1989). A modified version of the Pleasure Scale for Children termed the Experienced Pleasure Scale for Children (ePSC) was also administered, which differs from the original PSC in that it asks subjects to rate only the events and activities which they have experienced. The TEPS and PSC are NIMH-endorsed methods for the study of Reward Responsiveness (National Institute of Mental Health, 2018).

Statistical Analyses

Statistical analyses were conducted in R version 3.4.1.

Analytical Models Assessing the Divergent Validity of the ‘effort’ Construct

Campbell and Fiske’s multitrait-multimethod matrix was used to examine the divergent validity of the ‘effort’ construct from other PVS constructs (Campbell & Fiske, 1959). EEfRT measurements were compared to five other methods for assessing reward behavior constructs such as Reward Responsiveness, Reward Learning, and Reward Probability. For adults, these
three other methods included the DDT/PDT, IGT, and the TEPS. For children, the PSC/ePSC was used in place of the TEPS.

**Analytical Models Assessing Familial Correlations for EEfRT Performance**

The degree of sibling-sibling similarity was tested by paired-sample correlations using intraclass correlations as well as Spearman’s \( \rho \). For parent-child correlations, a linear regression model was used with child hard task choice percentage as the outcome (dependent) variable and mother and father hard task choice percentage as the predictor (independent) variables. Benjamini-Hochberg False Discovery Rate (FDR) correction was applied to correct for multiple comparisons, and \( p \)-values reported in the results are FDR-adjusted. This procedure is a recommended alternative to Bonferroni-type corrections, which are often criticized for increasing the likelihood of type-II errors, particularly when a large number of tests are conducted (Perneger, 1998).

**Analytical Models Assessing the Relationship between EEfRT and Psychopathology**

A series of zero-inflated negative binomial regression models examined ‘effort’ expenditure and reward sensitivity as predictors of psychopathology in adults. Zero-inflated negative binomial regression was used to account for non-normal distribution of the outcome variables, which were T-scores. The main effects of hard task choice percentage, reward sensitivity, and sex were tested. It also included the testing of interactions of sex with hard task choice percentage, and sex with reward sensitivity. All adult models covaried for demographic variables including age, education, employment, income, race, and marital status.

As with the adults, zero-inflated negative binomial regression was used to account for non-normal distribution of outcome variables in children. Main effects of hard task choice percentage, reward sensitivity, and sex were tested. Additionally, interactions between hard task
choice percentage and sex as well as reward sensitivity and sex were tested. All child models
covaried for parent income and education, but not age, as the range was limited and there was no
association between child’s age and EEfRT scores.

Robust standard errors were used across all models to account for non-independence in
the data due to familial relationships. The Benjamini-Hochberg False Discovery Rate method
(Benjamini & Hochberg, 1995) was used to correct for multiple testing. A 5% false discovery
rate was utilized for determining the significance of findings across both groups. For the
regression models, the total number of tests conducted was 12 for adults and 8 for children. \(P\)-
values reported in the results are false-discovery-rate adjusted.
Results

EEfRT Task Statistics

For children, the average proportion of hard task choices was 56.7%, and the average reward sensitivity was 0.11. Hard task choice is represented by the proportion of total trials in which the participant chose the hard task rather than the easy task. Reward sensitivity is an indicator of the degree to which reward magnitude (dollar amount) influences choosing the hard task vs. the easy task, where higher values indicated stronger influence. The minimum reward sensitivity was -3.3, and the maximum was 6.8. The inter-quartile range of reward sensitivity was -0.004 to 0.027. Mean percent completion rate among children was 86.6%. On average, child participants timed out in their choice of the hard vs. easy task in just 1.3% of trials.

Prior to administration of the EEfRT, adult participants were given a short questionnaire assessing their understanding of basic probability. Participants who did not demonstrate adequate understanding of probability were not allowed to participate in the EEfRT. For the adult participant sample, the average proportion of hard task choices was 36.4%, and the average reward sensitivity was 0.73. The minimum reward sensitivity was -2.0, and the maximum was 7.9. The inter-quartile range of reward sensitivity was 0.17 to 1.18. Mean percent completion rate among adults was 93.4%. If participants did not choose between the hard or easy task, that trial was marked as a ‘time-out’ and was not included in calculation of summary variables. For adults, 0.7% chose only easy tasks, and none chose only hard tasks. For children, 0.9% chose only easy tasks, and 3.1% chose only hard tasks. On average, adult participants timed out in their choice of the hard vs. easy task in 6.9% of trials.

In comparing EEfRT statistics between adults and children, we found that the average proportion of hard task choices was higher among children relative to adults (56.7% vs. 35.4%)
and the average reward sensitivity value was lower among children relative to adults (0.11 vs. 0.73).

**Effort Construct Validity**

In adults, the EEfRT outcome variables of hard task choice and reward sensitivity were correlated with one another ($r = 0.33$, $p = 0.00$). In children, the EEfRT outcome variables of hard task choice and reward sensitivity were also correlated ($r = 0.31$, $p = 0.00$). For both adults and children, neither EEfRT outcome variable was significantly correlated with any other reward behavior measure items. In adults, the ‘effort’ hard task choice was not significantly correlated with PDT area under the curve ($r = -0.09$, $p = 0.70$), DDT area under the curve ($r = 0.08$, $p = 0.70$), IGT totals (Latency: $r = -0.02$, $p = 0.70$; Net Gain: $r = 0.09$, $p = 0.70$), and TEPS subscales (Anticipatory: $r = 0.12$, $p = 0.10$; Consummatory: $r = 0.05$, $p = 0.10$). Similarly, the EEfRT outcome variable of reward sensitivity had very weak and non-significant correlations with PDT area under the curve ($r = -0.04$, $p = 0.70$), DDT area under the curve ($r = 0.00$, $p = 0.70$), IGT totals (Latency: $r = 0.03$, $p = 0.70$; Net Gain: $r = 0.05$, $p = 0.70$), and TEPS subscales (Anticipatory: $r = 0.10$, $p = 0.10$; Consummatory: $r = 0.02$, $p = 0.10$) (**Figure 3.1A**). In children, the ‘effort’ hard task choice was not significantly correlated with PDT area under the curve ($r = 0.00$, $p = 0.70$), DDT area under the curve ($r = -0.03$, $p = 0.70$), Pleasure subscales (Consummatory: $r = 0.05$, $p = 0.10$; Anticipatory: $r = 0.02$, $p = 0.10$), and IGT totals (Latency: $r = -0.01$, $p = 0.70$; Net Gain: $r = -0.05$, $p = 0.70$). Similarly, the EEfRT outcome variable of reward sensitivity had no significant correlations with PDT area under the curve ($r = 0.00$, $p = 0.70$), DDT area under the curve ($r = 0.03$, $p = 0.70$), Pleasure subscales (Consummatory: $r = 0.07$, $p = 0.10$; Anticipatory: $r = 0.08$, $p = 0.10$), and IGT totals (Latency: $r = 0.03$, $p = 0.70$, Net Gain: $r = 0.03$, $p = 0.70$) (**Figure 3.1B**).
**Familial Correlations**

Small, but significant positive correlations were observed between siblings for hard task choice percentage ($r = 0.11, p = 0.001$). The father-child ($r = -0.087, p = 0.072$) and mother-child correlations ($r = -0.012, p = 0.71$) were not significant (Figure 3.2). For reward sensitivity, no
significant correlations were found between siblings \((r = 0.012, p = 0.72)\) or between father-child pairs \((r = 0.063, p = 0.054)\) or mother-child pairs \((r = 0.011, p = 0.62)\). No significant results were found when regressing child values on parent values for either hard task choice or reward sensitivity.
Figure 3.2. Paired correlations for EEfRT hard task choice % between parents and their children, and between siblings.
A main effect of hard task choice was observed in child models predicting attention problems, social problems, and withdrawn depression. Increased attention problems were observed among children who primarily chose the easy task over the hard task ($\beta = -1.51$, FDR-adjusted $p = 0.01$). Similarly, increased social problems were observed among children who primarily chose the easy task over the hard task ($\beta = -1.34$, FDR-adjusted $p = 0.03$). In addition, increased severity of withdrawn depression was observed among children who primarily chose the easy task over the hard task ($\beta = -0.95$, FDR-adjusted $p = 0.05$).

The interaction between sex and hard task choice was significant in the model predicting anxious depression. Among children who primarily chose the easy task over the hard task, males reported more anxious depression than females ($\beta = 0.92$, FDR-adjusted $p = 0.05$). Severity of anxious depression did not differ between males who preferred the easy task and males who preferred the hard task (High Hard Task % CBCL Score = 56.1; Low Hard Task % CBCL Score = 56.3); in contrast, severity of anxious depression was lower in females who preferred the easy task in comparison to females who preferred the hard task (High Hard Task % CBCL Score = 56.6; Low Hard Task % CBCL Score = 54.4). (Figure 3.3A).

We found a significant interaction between reward sensitivity and sex in the model predicting thought problems as follows: among children who primarily chose the easy task over the hard task, males reported more increased thought problems than did females ($\beta = -0.84$, FDR-adjusted $p = 0.004$). Similar to the model predicting anxious depression, severity of thought problems did not differ between males who preferred the easy task and males who preferred the hard task (High Reward Sensitivity CBCL Score = 56.8; Low Reward Sensitivity CBCL Score = 57.1), whereas severity of thought problems was lower in females who preferred the easy task in
comparison to females who preferred the hard task (High Reward Sensitivity CBCL Score = 56.7; Low Reward Sensitivity CBCL Score = 55.3). (Figure 3.3B).

**Figure 3.3.** Interaction effects between EEfRT measures and sex in models predicting psychopathology in children.

*Adult Psychopathology*

Models predicting adult psychopathology found variable results based on the reward probability level. At medium reward probability (50%), we observed a significant interaction between hard task choice and sex (β = 1.249, FDR-adjusted p = 0.008). At this probability level, among adults who primarily chose the hard task, females had greater severity of somatic complaints compared with males (Female ASR Somatic Complaints Score = 56.7; Male ASR Somatic Complaints Score = 55.2). At high reward probability (88%), we observed a significant
interaction between hard task choice and sex (β = 1.140, FDR-adjusted \( p = 0.007 \)). At this probability level, among adults who primarily chose the easy task over the hard task, males had greater severity of thought problems relative to females (Female ASR Thought Problems Score = 56.9; Male ASR Thought Problems Score = 58.0).

In models predicting reward sensitivity, a significant interaction between reward sensitivity and sex was observed in the model predicting tobacco problems (β = -0.637, FDR-adjusted \( p = 0.008 \)). Among adults who primarily chose the hard task, females had greater severity of tobacco problems compared with males (Female ASR Tobacco Problems Score = 52.5; Male ASR Tobacco Problems Score = 51.7). For adults who primarily chose the easy task, severity of tobacco problems across the sexes was not significantly different (Female ASR Tobacco Problems Score = 53.0; Male ASR Tobacco Problems Score = 53.3).
Discussion

The current study sought to empirically validate the ‘effort’ construct of Reward Valuation via behavioral assessments and self-reports, and to determine if ‘effort’ diverged from other constructs/constructs of reward behavior. We found that both measures of ‘effort’ (hard task choice and reward sensitivity) did not correlate with other measures of reward behavior. This divergence indicates that the ‘effort’ construct captures a distinct and specific element of human reward behavior. Our study is the first to demonstrate this divergence.

Based on evidence from the literature and from the initial findings in Study 1, we hypothesized that psychopathology scales linked to anxiety or depression would show significant associations with ‘effort’ measures. Additionally, we expected that such associations would present differently between males and females in effort-based decision making. In concordance with these hypotheses, hard task choice percentage was a significant predictor of both anxiety and thought problems in children and was moderated by sex. The consistency of these findings between Studies 1 and 2 for anxiety and thought problems indicate that aberrant ‘effort’ valuation may be a reliable predictor of psychopathologies associated with those problems, such as anxiety and depression. The additional consistency of the moderating effects of sex underscores the importance of incorporating sex-specificity in any research aimed at understanding dimensions of psychopathology, including diagnosis, biological mechanisms, and treatment. These findings serve to further support the validity of the ‘effort’ construct.

Our analysis also found differences in effort-based decision-making between male and female children regarding severity of psychopathology, based on associations with low ‘effort’ and reward sensitivity. At high ‘effort’ levels and reward sensitivity, males and females did not have a significant difference in CBCL Thought Problem T-score. However, at low ‘effort’ levels,
males had significantly higher CBCL Thought Problem T-scores than females, though the underlying reason for this divergence is not currently clear. According to the CBCL scale, Thought Problems include seeing or hearing things, repeating acts, and strange ideas/behavior. In children, this has been linked with relatively high sensitivity and specificity to behavior on the autism spectrum (Mazefsky et al., 2011). Previous research investigating diagnostic differences has shown that males are more likely to be diagnosed with ASD, with a male-to-female ratio of 3:1 (Loomes et al., 2017). However, previous research has also demonstrated that there are clear differences in clinical manifestation between males and females with ASD (Rynkiewicz & Łuczk A, 2018). The CBCL does not have an ASD-specific subscale, so our finding may, in part, be capturing this ASD-specific difference. However, our study found significant sex differences only at low ‘effort’ levels/reward sensitivity (impaired reward processing) but not high ‘effort’ levels/reward sensitivity (normal reward processing). This seems to indicate that there is some interaction specific to impaired reward processing that is worthy of further investigation. It is important to have a deeper understanding of how and why sex impacts reward processing, which could provide greater insight into ASDs, as well as other disorders where sex differences are present.

Our previous work on ‘effort’ in children in Study 1 demonstrated that ‘effort’ expenditure had a significant relationship with anxiety and thought problems that was moderated by sex. At low levels of ‘effort’ and reward sensitivity, male children had greater anxiety and thought problems than female children. There was also significant positive correlations between siblings’ ‘effort’ valuation, but no correlations between parents and their children (Nguyen et al., 2019). While these results may seem at odds with the familial nature of these types of psychopathology, previous research in child behavior has found that developmental shifts occur
in decision-making during adolescence (Hartley & Somerville, 2015). Specifically, the increase in risk-taking behavior is often attributed to extensive structural and functional brain development. Although risk-taking encompasses more than solely reward-based behavior, a previous study found evidence for increased limbic responses to reward stimuli which peaked at mid-adolescence, indicating that reward behavior is an affected component of adolescent development (Crone & Dahl, 2012). While our child participants were primarily in the pre-adolescent age range, previous research has found that adolescents and children take equal levels of risk (Defoe, Dubas, Figner, & Van Aken, 2015). Additionally, there are distinct methodological differences between child and adult tasks which cannot be discounted as a confounding source.

The current work faced constraints inherited from Study 1, including the use of parent-reports as measures for both child and parent psychopathology, and a disproportionate number of (adult) female participants. In addition, because of our sampling strategy that was agnostic to disorders, few participants displayed clinically elevated symptoms for some of the dimensions of psychopathology examined in this study. Future studies designed around collecting information from individuals who experience specific problems may help to discover new or clearer relationships between ‘effort’ valuation and specific forms of psychopathology.

While the current work demonstrated the applicability of construct-based validation and assessment towards ‘effort’ and its relationship to multiple types of psychopathologies, it also highlights areas of possible improvement. To our knowledge there has been no previous study of the relationship between ‘effort’ and child psychopathology. Many of the reward behavioral measurement tasks were developed and intended for adults, including Treadway’s EEfRT task. Because of this, it is not clear whether applying such tasks across both adults and children is
fully equivalent. We found significant sibling-sibling correlations but no significant parent-child correlation. This suggests that the child and adult EEfRT tasks do not measure the same familial construct. Additionally, the psychopathology models that were significant in children and the trends observed within those models differed from those found in adults. Given that our sample size is large, and the mother-child and father-child correlations are negligible (Mother-Child: \( r = -0.037, 95\% \text{ CI} = [-0.188, 0.115] \); Father-Child: \( r = -0.142, 95\% \text{ CI} = [-0.288, 0.004] \)), it is unlikely that our finding of non-significance was due to low power. Ideally, a longitudinal study would compare a child’s behavior to their parent’s historical behavior at a similar age. As such, we believe that longitudinal studies are essential to investigate the stability of ‘effort’ valuation and reward processing behavior over time, especially in children, who may exhibit differences as they pass through stages of their development. Our findings support longitudinal research as an important component to the goals of research-based validation of constructs and revision of current diagnostic systems. Modern day conceptualizations of psychiatric disorders may be more accurately reflected along spectra of illness severity, which more closely resemble dimensions of underlying behavioral and biological processes, rather than simply discrete phenomena, a direction consistent with the premise of the Research Domain Criteria (RDoC) initiative put forth by the U.S. National Institute of Mental Health.

The current findings show that ‘effort’ is a psychological construct that is both empirically valid and worthy of further study in the context of child psychopathology, with differing profiles of effect between sexes. Based on the observed associations between low ‘effort’ expenditure, low reward sensitivity, anxiety, and thought problems, we identified aberrant reward processing as a potentially important indicator of specific dimensions of psychopathology. Additionally, the reward processing deficits’ greater impact on male children
indicate that ‘effort’ expenditure and reward sensitivity may be important risk factors to assess and address in males and may be a critical target for mitigating symptom severity. It is possible that these are key to understanding the biological mechanisms behind psychopathological manifestations. In summary, our current study provided credible evidence supporting the further use of EEfRT to understand ‘effort’ valuation in children, especially if applied in a longitudinal approach, to determine the stability of the construct over time as children progress through development to adulthood.
### Appendix Chapter 3

#### Supplementary Table 3.1. Participant Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Parents (N = 1270)</th>
<th>Children (N = 1536)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean +/- SD)</td>
<td>37.4 years ± 6.9</td>
<td>9.0 years ± 3.1</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>69%</td>
<td>49%</td>
</tr>
<tr>
<td>Race (% white)</td>
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<td></td>
</tr>
<tr>
<td>(% black)</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>(% two or more races)</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>(% other)</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (% Hispanic)</td>
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</tr>
<tr>
<td>Psychiatric (% psychiatric history)</td>
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</tr>
<tr>
<td>Education (% less than HS)</td>
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<td>(% some college/post-secondary non-</td>
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<td>(% would rather not say)</td>
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<td>Race (% black)</td>
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<tr>
<td>(% other)</td>
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<td>Psychiatric (% psychiatric history)</td>
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<td><strong>Families (N = 1215)</strong></td>
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**Supplementary Table 3.2. Psychopathology Details**

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<th>Psychopathology Evaluation</th>
<th>Clinically Significant (%)</th>
<th>Mean +/- SD</th>
<th>Range</th>
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<tr>
<td><strong>Anxious-Depressed</strong></td>
<td>19.3%</td>
<td>56.7 ± 9</td>
<td>48</td>
</tr>
<tr>
<td><strong>Withdrawn</strong></td>
<td>17.2%</td>
<td>56.1 ± 8</td>
<td>50</td>
</tr>
<tr>
<td><strong>Somatic Complaints</strong></td>
<td>17.9%</td>
<td>56.4 ± 8</td>
<td>50</td>
</tr>
<tr>
<td><strong>Thought Problems</strong></td>
<td>17.2%</td>
<td>56.7 ± 8</td>
<td>48</td>
</tr>
<tr>
<td><strong>Attention Problems</strong></td>
<td>17.2%</td>
<td>56.4 ± 8</td>
<td>45</td>
</tr>
<tr>
<td><strong>Aggressive Behavior</strong></td>
<td>18.5%</td>
<td>57.0 ± 8</td>
<td>48</td>
</tr>
<tr>
<td><strong>Rule-Breaking Behavior</strong></td>
<td>14.8%</td>
<td>55.5 ± 7</td>
<td>39</td>
</tr>
<tr>
<td><strong>Intrusive</strong></td>
<td>6.3%</td>
<td>53.3 ± 5</td>
<td>25</td>
</tr>
<tr>
<td><strong>Internalizing Problems</strong></td>
<td>19.3%</td>
<td>52.3 ± 13</td>
<td>70</td>
</tr>
<tr>
<td><strong>Externalizing Problems</strong></td>
<td>15.8%</td>
<td>52.6 ± 12</td>
<td>65</td>
</tr>
<tr>
<td><strong>Tobacco Times Per Day</strong></td>
<td>1.9%</td>
<td>52.7 ± 5</td>
<td>50</td>
</tr>
<tr>
<td><strong>Alcohol Days Drunk</strong></td>
<td>9.9%</td>
<td>53.8 ± 7</td>
<td>50</td>
</tr>
<tr>
<td><strong>Drugs Days Used</strong></td>
<td>9.1%</td>
<td>52.6 ± 8</td>
<td>50</td>
</tr>
<tr>
<td><strong>Mean Substance Use</strong></td>
<td>9.9%</td>
<td>54.6 ± 6</td>
<td>37</td>
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</tbody>
</table>

<table>
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<th><strong>Child Behavior Checklist (CBCL)</strong></th>
<th>Clinically Significant (%)</th>
<th>Mean +/- SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anxious-Depressed</strong></td>
<td>17.8%</td>
<td>55.7 ± 8</td>
<td>42</td>
</tr>
<tr>
<td><strong>Withdrawn-Depressed</strong></td>
<td>17.7%</td>
<td>56.2 ± 8</td>
<td>44</td>
</tr>
<tr>
<td><strong>Somatic Complaints</strong></td>
<td>13.6%</td>
<td>54.8 ± 7</td>
<td>44</td>
</tr>
<tr>
<td><strong>Social Problems</strong></td>
<td>17.5%</td>
<td>56.4 ± 8</td>
<td>46</td>
</tr>
<tr>
<td><strong>Thought Problems</strong></td>
<td>19.6%</td>
<td>56.5 ± 8</td>
<td>36</td>
</tr>
<tr>
<td><strong>Attention Problems</strong></td>
<td>24.9%</td>
<td>57.5 ± 9</td>
<td>47</td>
</tr>
<tr>
<td><strong>Rule-Breaking Behavior</strong></td>
<td>19.4%</td>
<td>56.3 ± 8</td>
<td>37</td>
</tr>
<tr>
<td><strong>Aggressive Behavior</strong></td>
<td>23.9%</td>
<td>57.3 ± 9</td>
<td>50</td>
</tr>
<tr>
<td><strong>Internalizing Problems</strong></td>
<td>18.4%</td>
<td>52.0 ± 12</td>
<td>52</td>
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<tr>
<td><strong>Externalizing Problems</strong></td>
<td>23.2%</td>
<td>53.2 ± 12</td>
<td>55</td>
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Chapter 4: Study Three – Genetic Contributions of Effort in Children and Adults

Introduction

Within the field of mental health research, there has been an increasing push to identify the genetic, neurohormonal, and physiological factors that predispose certain individuals to maladaptive psychological states. Along this line of inquiry, the Research Domain Criteria (RDoC) initiative established by the U.S. National Institute of Mental Health (NIMH) has served as a driving force for discussion and investigation. The initiative identifies six broad “domains” of human psychological functioning—such as cognitive systems and social processes—that can be studied at various “units of analysis”; these units of analysis include genes, molecules, circuits, and behaviors, among others. An important aspect of this framework is that it views psychopathology as extreme deviations from normal psychological function, allowing for a view of mental illness that goes beyond diagnostic thresholds and boundaries. This approach contrasts with the earlier “endophenotype” approach, which supposed that intermediate traits (such as the units of human psychological functioning mentioned above) were specific to different forms of psychopathology. RDoC instead implicitly assumes that such functions will span diagnostic boundaries, an important distinction, as the endophenotype concept did not hold up upon empirical evaluation. Recent research assessing the utility of the endophenotype concept conducted a replication study of 17 endophenotypes from previously reported literature and found that none were associated with genetic variants that had large effect sizes. This research ultimately concluded that these endophenotypes much more closely resembled polygenic complex traits akin to traditional genetic biomarkers that associate with medically relevant conditions (such as cholesterol level, body mass index, and heart rate) rather than the disorder-specific, diagnostically confirmatory traits they purported to be (Iacono, 2018).
Positive Valence Systems (PVS) is the name of the RDoC domain encompassing reward-related functions and positive motivation states. Within the PVS domain there are three recognized “constructs”—reward responsiveness, reward learning, and reward valuation—that are further divided into nine “subconstructs.” Overall, the PVS domain remains relatively understudied compared to other domains such as the Negative Valence Systems domain (concerning responses to aversive situations) and the Cognitive Systems domain. The objective of this study, therefore, is to further investigate this domain in the context of psychopathology.

Abnormalities in reward-related functioning have been observed in many psychiatric illnesses, with some being marked by blunted reward processing and others by heightened reward processing. Major depressive disorder (MDD), schizophrenia (SCZ), and substance use disorders (SUDs) have all been correlated with decreased responsiveness to reward, although the exact pattern behind this blunted response differs between disorders (Nusslock & Alloy, 2017). Self-report studies conducted on individuals with MDD and SCZ have consistently found that these individuals are less likely to report enjoyment of pleasurable stimuli (Segarra et al., 2016; Vrieze et al., 2013). MDD has also been correlated with a decreased willingness to expend physical effort to obtain monetary reward (Treadway et al., 2012). An imbalance between anticipation and consumption of rewards has been observed in SUDs, where reward motivation is increased despite lesser enjoyment when consuming the reward (Robinson & Berridge, 2001). In contrast, individuals with attention-deficit/hyperactivity disorder (ADHD) have consistently been found to experience heightened discounting of future rewards (i.e., these individuals undervalue future rewards, predisposing them to impulsive choices of short-term rewards). This temporal discounting in ADHD may be associated with the observed hyporesponsiveness of certain reward circuitry during reward anticipation (namely, the ventral striatum) (Rubia, 2018).
Heightened reward processing leading to increased reward anticipation and greater drive to obtain rewards has been observed in bipolar disorder (BPD), externalizing disorders, and SUDs. In neuroimaging studies, externalizing problems, such as impulsive antisocial traits, have also been associated with abnormal function in reward circuitry such as the ventral striatum, characterized as hypersensitivity to reward cues (Murray, Waller, & Hyde, 2018). Individuals with BPD show increased willingness to work for rewards despite exhibiting normal reward responsiveness and learning (Nusslock & Alloy, 2017). Heightened anticipatory response to drugs and other addiction-related rewards seems to drive individuals with SUDs to excessively pursue these rewards despite the severe costs often associated with such behaviors, which contrasts with the blunted actual response to reward described previously (Leyton, 2014).

Overall, SUDs provide an interesting perspective on the role of reward processing in psychological function and behavior, as they do not easily lend themselves to unitary theories supporting generalized hypo- or hyper-active reward processing. A maladaptive scaling hypothesis, by which stimuli are continually compared to rewarding “anchors,” has been proposed to better explain SUDs and other conditions. Similar to how an individual values $50 less when he/she is aware that he/she could have earned $500, individuals with SUDs would be understood to experience hyporeward processing regarding everyday stimuli as compared to the objects of their addiction. Importantly, this theory still allows for hyperreward processing of the object of addiction itself (Zald & Treadway, 2017).

Ultimately, it has been consistently demonstrated that reward abnormalities are a prominent feature of many forms of psychopathology, although the exact biological source(s) for these aberrations is still the subject of much research. As such, an RDoC-based investigation into the genetic basis of reward behavior and how those genes connect to dimensions of
psychopathology would serve to both test application of the RDoC research framework and advance our understanding of psychiatric illness.

Although “genes” have been identified as the lowest-level unit of analysis within the RDoC system, the NIMH has removed any references to specific genes from the current version of the RDoC matrix, citing the need for more robust evidence of association. With this need in mind, genome-wide association studies (GWAS) have been employed as an unbiased means to identify genes related to mental phenomena, including RDoC constructs. One particularly promising tool in psychiatric genetic research has been the polygenic risk score (PRS). Instead of relying solely on identifying individual genes that meet the standard for genome-wide significance, the polygenic risk score considers the combined effect of hundreds (or even thousands) of genes that have more modest effects on a phenotype. The PRS is a concise individualized score that can then be correlated with disorder status, metrics of brain morphology, and even responses to self-report tasks. Utilizing disorder-agnostic, quantitative metrics of psychological function (rather than diagnostic classification) is a more RDoC-aligned approach to genomic studies. The use of such phenotypes in GWAS studies is relatively rare but has become increasingly popular within the past few years, especially in research on reward behavior. A study of 23,217 research participants of European ancestry identified several candidate genes linked to performance on the Monetary Choice Questionnaire, a behavioral task based on the concept of delay discounting (DD) (Sanchez-Roige et al., 2017). Linkage disequilibrium score regression (LDSR) analyses found that DD was positively genetically correlated with ADHD and MDD, and negatively genetically correlated with SCZ. Noting that such results were unexpected given the previously established positive correlation between ADHD and SCZ, the authors explained that such findings may highlight the usefulness of the
RDoC approach. Indeed, such results may indicate differences with regards to DD despite similarities with regards to other aspects of disorder etiology.

While genetic variants and PRS are an important component to understanding reward behavior and psychopathology, the larger picture of biological and functional pathways are another point of analysis that is important to consider. Gene-set analysis aggregates individual genes to groups sharing certain biological, functional, or other characteristics, and can make it possible to detect effects consisting of multiple weaker associations (de Leeuw, Mooij, Heskes, & Posthuma, 2015). Multiple pathways are known to be involved in the complex processes underlying reward behavior, forming a circuit which is generally understood to be the biological basis for reward and decision-making. This reward circuit includes brain structures such as the striatum, orbitofrontal cortex, and amygdala, and biological pathways such as those involved in dopamine receptor signaling or modulation of such signaling (Schultz, 2015). If indeed quantitative measures of reward behavior are associated with genetic sources, gene-set enrichment analysis is an additional method for assessing this connection via gene-sets based on reward circuit components.

The Effort Expenditure for Rewards Task (EEfRT) was developed by Treadway and colleagues to measure effort-based decision-making, and is specifically endorsed by the NIMH as a method for study of PVS reward constructs (Treadway et al., 2009). Outcome measures from this task are designed to capture participants’ willingness to work to obtain rewards and their sensitivity to changes in those rewards. This task has previously been used successfully in behavioral studies, in both traditional designs aimed at assessing specific forms of psychopathology such as SCZ and MDD (Treadway et al., 2012, 2015), as well as in RDoC-based study designs utilizing a disorder-agnostic approach (Nguyen et al., 2019). EEfRT
measures have been found to be significantly associated with each of the different types of psychopathologies mentioned previously, where reward processing is known to be impacted (MDD, SCZ, ADHD, SUDs, etc.). Given the evidence above of known links between reward behavior and psychopathology, and the need within the RDoC system for gene-based research, especially in the understudied constructs of the PVS, we chose to design a study that would uniquely address all of those needs simultaneously. The present study was a family-based genetic study of reward behavior and psychopathology. We collected quantitative behavioral data via the EEfRT, and genotyped children and their parents, to investigate the genetic basis of effort-based reward behavior and to determine how that associated with assessments of psychopathology. The methodological approach of the current study is unique, breaking from traditional case/control GWAS, instead opting for quantitative variables in the generation of and correlations with polygenic risk scores. The result is a higher-powered analysis that is ultimately more reflective of natural tendencies and presentations. This study also marks the first GWAS conducted using measures from the EEfRT task, and correlations identified within the current study provide valuable information towards further evaluation and revision of RDoC constructs. These findings lay the foundation for further RDoC-based research into clinical and subclinical maladaptive reward-related psychological function.
Materials and Methods

Note: Given that this Study 3 uses the same participant sample from Study 2, some of the following sections reuse descriptions from the ‘Materials and Methods’ section in Chapter 3. They have been repeated for the convenience of the reader as they are still components of the analyses of Study 3. Sections with no consequential changes relative to their Chapter 3 counterparts have been marked with an asterisk (*) for transparency.

Procedure*

Participants were recruited from a variety of sources within the Syracuse, NY and surrounding areas, including the Child and Adolescent Psychiatry Clinic at SUNY Upstate Medical University, child psychiatrists and mental health clinicians working in private practice, and community events (local fairs, festivals, etc.). Children meeting the following criteria were excluded from the study due to their possible confounding influence on results: adopted, sensorimotor disability, a diagnosed neurological condition, a history of head injury with documented loss of consciousness lasting more than 10 minutes, an uncontrolled medical condition, or an inability to understand the English language. For adults, the same exclusion criteria were applied, except adoption. Two additional exclusion criteria were also added to the adult exclusion list: people who did not have the ability to independently complete study tasks, and women who were pregnant or gave birth within 6 months prior to the study visit. At the time of ascertainment, pregnant women were traditionally considered to be part of a ‘vulnerable’ population, with a compromised ability to protect their interests and provide informed consent (Blehar et al., 2013).

An estimate of intelligence quotient (IQ) was obtained from scores on the vocabulary and abstraction subtests of the Shipley-2 (a validated, age-appropriate instrument for subjects
between the ages of 7 and 89 years) (Kaya et al., 2012). This was applied to both adults and children within the recommended age range. As the mean of these two tests correlates 0.90 with full-scale IQ, subjects with an estimated IQ below 80 were excluded from this study. Informed consent was obtained from all parents and assent was given by all children upon arrival for their study visit, and the study was approved by the Upstate Medical University Institutional Review Board.

Participants*

A total of 2806 participants (1536 children and 1270 parents) met eligibility criteria and took part in this study. The study required parents to report both for themselves and for their children whether they had ever sought mental health care for emotional or behavioral problems, and it was reported that 52% of children and 52% of parents had such psychiatric history. Our study population was drawn from a convenience sample that was purposely enriched for psychopathology via recruitment in local clinics to ensure a broad range of psychopathology into both the clinical and normal ends of the distribution. Psychiatric participants were not selected based on any particular form of psychopathology, as our study was designed to employ an agnostic ascertainment scheme consistent with an RDoC-based approach. All children were between the ages of 6 and 12 years (mean age = 9, S.D. = 3.1), and their parents were between the ages of 23 and 59 years (mean age = 37, S.D. = 6.9). Parental age was capped at 59 years of age to avoid the possibility of age-related cognitive decline, as previous literature has indicated that cognitive decline most commonly occurs starting at 60 years of age (Salthouse, 2010). Although there is a possibility of including participants who are already experiencing cognitive decline by placing our age cap at the edge of cognitive decline onset, given that only 3.1% of adult participants were over 50 years of age, we do not believe that this is a significant enough
proportion for our results to be influenced by aging. While there were approximately equal numbers of female and male children (49% vs. 51%), significantly more of the participating parents were female than male (69% vs. 31%). Participants were diverse in race, with 65% of parents identifying as White, 24% Black, and 11% other or multiple races, and 55% of children identifying as White, 25% Black, and 20% other or multiple races. Additionally, 6% of parents and 11% of children were Hispanic. The dataset includes 955 different families, with an average size of 2.94. Since 25% of participants chose not to report their household income, multiple imputation was utilized to handle missing adult income data. Ten iterations of imputation were conducted. Demographic information including education, employment, marital status, age, IQ, ancestry, and sex were used to predict income in the imputation procedure. When modeled together, these variables explained a large proportion of the variance in income ($R^2 = 0.698$).

Detailed demographic information is available in in Appendix Chapter 4 Supplementary Table 4.1.

Measures

**Biological Sample Acquisition**

Study visits were approximately 3 hours in length and involved the completion of a variety of computerized inventories and behavioral paradigms. At the time of this study visit, whole blood samples were obtained from subjects by a licensed phlebotomist. Adults had a minimum of 5 mL of blood drawn into two 8.5 mL ACD tubes and one 10.0 mL EDTA tube. Children up to 50 lbs. had blood drawn into two 2.6 mL ACD blood tubes and one 3.0 mL EDTA blood tube, and children between 51 lbs. and 100 lbs. had three 6 mL blood tubes drawn (both ACD and EDTA). Samples were obtained this way for both contribution to this study as well as deposition in the NIMH repository. For study participants who had ethical or other
objections to blood-sample collection, a saliva sample was obtained instead. Saliva samples were collected via Norgen Saliva Collection and Preservation devices according to device instructions.

Effort Expenditure for Rewards Task: Reward Sensitivity and Motivation*

The Effort Expenditure for Rewards Task (EEfRT) was developed by Treadway and colleagues to measure effort-based decision-making (Treadway et al., 2009). The EEfRT consists of a multi-trial game in which participants attempt to maximize their monetary rewards. The rules of the game were explained to each subject as follows: 1) They were instructed to choose between two types of tasks for each trial (‘Easy Task’ or ‘Hard Task’), where the ‘Hard Task’ provided the opportunity for much greater monetary gain relative to the ‘Easy Task’; 2) The ‘Easy Task’ required 30 button presses with the dominant index finger within 7 seconds for a fixed reward value of $1.00; 3) The ‘Hard Task’ required 100 button presses with the non-dominant fifth finger within 21 seconds for a varying assigned reward value between $1.24 and $4.30; 4) Subjects were expected to complete multiple trials and were given a 20-minute time limit to complete as many trials as they could; 5) For the adult trials, three levels of probability were presented for obtaining a reward upon successful trial completion: ‘high’ (88%), ‘medium’ (50%), and ‘low’ (12%). This means that some adult trials did not result in a reward, even if the subject successfully completed the task. According to Treadway and colleagues, this probability component is designed to add complexity to the decision-making aspect of selecting the task difficulty, to ensure that neither a strategy of choosing only the easy or hard options would lead to ‘optimal’ performance. With this safeguard in place, subjects’ decisions better reflect individual differences in willingness to expend ‘effort’ for a given level of reward (Treadway et al., 2009). However, since this component required the subjects to have a complete understanding of the concept of probability and its effect on the reward outcome to properly
impact the decision-making process, it was not practical to apply to child participants given their young age. As a result, the probability component is not present in the child version of the EEfRT task. All subjects received trials presented in the same randomized order. If participants did not choose between the hard or easy task, the trial was marked as a ‘time-out’ and was not included in the calculation of summary variables.

Our outcome variables for the EEfRT task were hard-task choice percentage and reward sensitivity. The hard-task choice percentage was calculated as the percentage of trials for which that participant chose the hard task. To derive reward sensitivity, a logistic beta weight was calculated on a per-participant basis via logistic regression with an individual’s hard task choice as the outcome (dependent) variable and reward magnitude (monetary amount; dollars) as the predictor (independent) variable. Therefore, the reward sensitivity variable is a measure of the degree to which the reward amount influences an individual’s choice between hard and easy tasks.

**Adult Self Report: Dimensional Measures of Psychopathology**

The Adult Self Report (ASR) was used to measure psychopathology in adult participants. This 126-item self-report measure is well validated and widely used in clinical practice and research to assess symptoms of psychopathology and adaptive functioning in individuals aged 18-59 years (Rescorla & Achenbach, 2004). Participants were asked to respond to each item on a three-point scale: from *not true*, *often true*, or *very true*, within the past 3 months. The ASR provides T-scores for seven syndrome scales (anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behavior, and rule-breaking behavior), three composite scores (internalizing composite, externalizing composite, and total problems composite), and four scales assessing substance use (tobacco, alcohol, recreational
drugs, and substance use composite). Due to the nature of the ASR assessment, the minimum possible T-score generated is 50, which would represent a participant whose level of self-reported psychopathology is that of a typically developing, psychiatrically unaffected individual (no psychopathology). A T-score of 50 then represented a ‘zero-value’ in our study.

Child Behavior Checklist: Dimensional Measures of Psychopathology*

The Child Behavior Checklist (CBCL) was used to measure psychopathology in children. This 113-item parent-report measure is well validated and widely used in clinical practice and research to assess emotional and behavioral functioning in children ages 6-18 years (Achenbach, 1991). Parents were asked to respond to each item on a three-point scale: from not true, often true, or very true, which indicated how true the item is for their child within the past 3 months. The CBCL provides T-scores for eight syndrome scales (anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior), and three composite scores (internalizing composite, externalizing composite, and total problems composite). The CBCL shares the same minimum T-score as the ASR (50), so our outcome variables follow the same logic described in the section above.

Biological Sample Genotyping

DNA purification was performed by the PsychGENe Lab at SUNY Upstate Medical University and at RUCDR at Rutgers University. DNA was extracted from whole-blood samples using PAXGENE DNA tubes and kits or saliva samples using Norgen Biotek tubes and kits, according to the manufacturer’s instructions. Genotypes were generated at the Broad institute using the Illumina Global Screening Array. Genetic variants were filtered out based on minor allele frequency (MAF < 1%), Hardy-Weinberg disequilibrium (P < 1 x 10^-6), and SNP call rate
(< 95%). Individual QC was based on missingness (>5%). Polygenic risk scores (PRSs) were constructed as the sum of risk alleles weighted by their effect size (Choi, Mak, & O’Reilly, 2020). A separate PRS per subject was calculated per EEfRT measure with different $P$ value inclusion thresholds ($P$-values: <0.01, <0.05, <0.1, <0.2, <0.3, <0.4, <0.5). Starting from a low $P$-value up to a $P$-value of 0.5, an optimal $P$-value threshold of 0.2 was identified based on model fit for highest phenotypic variance explained.

Statistical Analyses

Quantitative Trait Association Analyses

Quantitative association analyses were performed via PLINK for EEfRT hard task choice and EEfRT reward sensitivity (Purcell et al., 2007). These analyses were performed separately for our adult and child populations. For each population, two sets of analyses were conducted, one without any covariates, and one using six ancestry principal components and demographic variables including age, education, employment, income, and marital status as covariates. Analyses without covariates were included to demonstrate the extent to which our findings were reliant on the presence of covariates. Linkage disequilibrium clumping was performed after association testing to ensure reported genetic signals were independent.

Gene-Level and Gene-Set Level Analyses

Gene-based association analyses were performed using MAGMA, a multiple regression framework that associates a continuous or binary trait variable to GWAS gene-level $p$-values. We ran four separate analyses, utilizing one of our continuous EEfRT outcome variables as the GWAS phenotype for each analysis in adults and then in children, and generated gene-level $p$-values by computing mean SNP association using the default gene model (SNP-wise=mean) with ± 10-kb extensions of gene boundaries and filtering on SNPs with minor allele frequency
Gene-level test statistics for each annotation were regressed on the corresponding gene annotation variable while adjusting for demographic and principal component covariates. Gene-set analyses were also used to investigate which sets of biologically related genes displayed the strongest evidence of association. Six different reward circuit-related gene sets were obtained from the Molecular Signatures Database (MsigDB) derived from the Gene Ontology (GO) Biological Process (BP) ontology: GOBP Forebrain Development, GOBP Midbrain Development, GOBP Limbic System Development, GOBP Dopamine Receptor Signaling, GOBP Neuron Glial Cell Signaling, and GOBP Response to Cocaine.

Analysis of the Association between EEfRT Quantitative PRSs and Psychopathology

A series of regression analyses examined our EEfRT-based quantitative PRSs as predictors of psychopathology in adults and children. Zero-inflated negative binomial regression was used to account for non-normal distribution of the outcome variables, which were T-scores from the ASR for adults and CBCL for children. The main effects of PRS, and the interaction effects of sex with PRS were tested. All adult models covaried for six ancestry principal components as well as demographic variables including age, education, employment, income, race, and marital status. All child models covaried for six ancestry principal components, parent income and education, but not age, as the range was limited and there was no association between child’s age and EEfRT scores.

Robust standard errors were used across all models to account for non-independence in the data due to familial relationships. The Benjamini-Hochberg False Discovery Rate method (Benjamini & Hochberg, 1995) was used to correct for multiple testing. A 5% false discovery rate was utilized for determining the significance of findings across both groups. For the
regression models, the total number of tests conducted was 12 for adults and 8 for children. *P*-values reported in the results are false-discovery-rate adjusted.
Results

EEfRT Task Performance Statistics

For children, the average proportion of hard-task choices was 56.7%, and the average reward sensitivity was 0.11. Hard task choice is represented by the proportion of total trials in which the participant chose the hard task rather than the easy task. Reward sensitivity is an indicator of the degree to which reward magnitude (dollar amount) influences choosing the hard task vs. the easy task, where higher values indicated stronger influence. The minimum reward sensitivity was -3.3, and the maximum was 6.8. The inter-quartile range of reward sensitivity was -0.004 to 0.027. Mean percent completion rate among children was 86.6%. On average, child participants timed out in their choice of the hard vs. easy task in just 1.3% of trials.

Prior to administration of the EEfRT, adult participants were given a short questionnaire assessing their understanding of basic probability. Participants who did not demonstrate adequate understanding of probability were not allowed to participate in the EEfRT. For the adult participant sample, the average proportion of hard-task choices was 36.4%, and the average reward sensitivity was 0.73. The minimum reward sensitivity was -2.0, and the maximum was 7.9. The inter-quartile range of reward sensitivity was 0.17 to 1.18. Mean percent completion rate among adults was 93.4%. If participants did not choose between the hard or easy task, that trial was marked as a ‘time-out’ and was not included in calculation of summary variables. For adults, 0.7% chose only easy tasks, and none chose only hard tasks. For children, 0.9% chose only easy tasks, and 3.1% chose only hard tasks. On average, adult participants timed out in their choice of the hard vs. easy task in 6.9% of trials.

Quantitative Trait Association Analyses
In adults, the strongest association for EEfRT hard task choice in the analysis without covariates was on chromosome 1 at an intronic SNP (rs17111676) within USP24, which reached genome-wide significance after clumping (i.e., grouping SNPs within 250 kb of the index SNP that have $r^2>0.2$ with the index SNP as implemented in PLINK) (Figure 4.1a). This SNP was also significant at a genome-wide level in association testing that included demographic covariates (Figure 4.1b). Additionally, 555 other SNPs reached the threshold of genome-wide suggestive evidence of association when not including demographic covariates, and 93 other SNPs reached the threshold for the genome-wide suggestive evidence of association when including covariates. These SNPs comprised both intergenic and intragenic loci across chromosomes 1 – 22. Most of the intragenic loci from these suggestive SNPs were located within introns, with a few located in promoters (Appendix Chapter 4 Supplementary Table 4.2).
Figure 4.1. Manhattan plots for EEfRT Hard Task Choice quantitative association test results with (A) and without covariates (B). Red horizontal line indicates genome-wide significant level ($p < 5 \times 10^{-8}$), blue horizontal line indicates genome-wide suggestive level ($p < 10^{-5}$).
The strongest association for EEfRT reward sensitivity in the analysis without covariates was on chromosome 4 within \textit{RNF150} and chromosome 5 within \textit{LOC105377703} at intronic SNPs (\textit{rs78629407}, \textit{rs183967064}), which were genome-wide significant after clumping (Figure 4.2a). These SNPs were also significant at a genome-wide level in association testing that included demographic covariates (Figure 4.2b). Additionally, for this reward sensitivity variable, 248 other SNPs reached the threshold of genome-wide suggestive evidence of association when \textit{not including} demographic covariates, and 202 other SNPs reached the threshold for genome-wide suggestive association when \textit{including} covariates, comprised again of both intergenic and intragenic loci across all autosomes (Appendix Chapter 4 Supplementary Table 4.3).
Figure 4.2. Manhattan plots for EEfRT reward sensitivity quantitative association test results with (A) and without covariates (B). Red horizontal line indicates genome-wide significant level ($p < 5 \times 10^{-8}$), blue horizontal line indicates genome-wide suggestive level ($p < 10^{-5}$).
In children, when testing for association between SNPs and E EfRT hard task choice, no SNP reached genome-wide significance (either with or without demographic covariates). However, 322 SNPs met the threshold for genome-wide suggestive evidence of association. Also, in testing for association between SNPs and E EfRT reward sensitivity, no SNP reached genome-wide significance (either with or without demographic covariates), while 641 SNPs met the threshold for genome-wide suggestive evidence of association.

**MAGMA Gene-Level and Gene-Set Analyses**

Gene-based association analysis was performed using MAGMA, testing first for joint association of all markers within a locus. This gene-level analysis yielded no genes surpassing the significance threshold but did demonstrate a few hundred genes meeting the suggestive threshold for each chromosome. To further examine if an aggregated effect was present, gene-set analysis was performed using 6 different reward processing-related gene sets. The following describes results from the analyses utilizing adult data, as no significant results were found in the analyses using child data. For the gene set involving “dopamine receptor signaling” and quantitative GWAS data using E EfRT hard task choice, significant associations after false-discovery rate correction were found on chromosomes 3 ($\beta = 1.33$, FDR-adjusted $p = 0.03$), 16 ($\beta = 1.01$, FDR-adjusted $p = 0.02$), and 17 ($\beta = 0.95$, FDR-adjusted $p = 0.04$). Significant associations were also found for the “forebrain development” gene set on chromosome 2 ($\beta = 0.43$, FDR-adjusted $p = 0.00$) and the “limbic system development” gene set on chromosome 2 ($\beta = 0.63$, FDR-adjusted $p = 0.02$). Lastly, significant associations were also found for the “response to cocaine” gene set on chromosomes 3 ($\beta = 1.08$, FDR-adjusted $p = 0.03$), 6 ($\beta = 1.05$, FDR-adjusted $p = 0.01$), and 8 ($\beta = 1.29$, FDR-adjusted $p = 0.03$). Gene-set analysis was
also performed using quantitative GWAS data using EEfRT reward sensitivity, but no significant gene-set associations were found after false-discovery rate correction.

**Models Predicting ASR/CBCL Psychopathology Score from Polygenic Risk Scores**

No significant main effects were found in models relating the quantitative PRS generated from EEfRT hard-task choice percentage to child psychopathology. The interaction between sex and quantitative PRS generated from EEfRT hard-task choice was significant in the model predicting attention problems. Significant association between PRS and higher severity of attention problems was found among male children, whereas no such trend was present for female children ($\beta = -48.5$, FDR-adjusted $p = 0.03$). We also found a significant interaction between sex and quantitative PRS generated from EEfRT hard-task choice in the model predicting withdrawn problems. Like the attention problems model, the association between PRS and higher severity of withdrawn problems was male-specific, with no trend seen in females ($\beta = -39.8$, FDR-adjusted $p = 0.02$).

No significant main effects or interactions were found in models relating quantitative PRSs generated from EEfRT reward sensitivity to child psychopathology.

No significant main effects or interactions were found in models relating our quantitative PRSs to adult psychopathology for either EEfRT hard task choice or EEfRT reward sensitivity.
Discussion

In recent years, the concept of using quantitative measures of elemental traits of human function to investigate the biological basis of psychopathology has gained increasing attention. Research has also demonstrated that abnormalities in complex phenotypic traits, such as reward behavior, are present across traditional diagnostic boundaries. The RDoC initiative aims to promote a combination of these two styles of approach, but subsequent revisions to the RDoC system specifically recognized the need for robust evidence of genetic association to constructs of human behavior. In this study, we began to address this need via genetic analysis of an RDoC-endorsed quantitative measure of effort-based reward behavior (EEfRT), in a sample not selected for any particular form of psychopathology. Our research aligns as closely as possible with the approach proposed by the RDoC initiative and our findings can provide an important baseline and support for future research efforts in this area.

We identified genetic loci on Chr1 (rs17111676), Chr4 (rs78629407), and Chr5 (rs183967064) that were significantly associated with quantitative measures of effort-based reward behavior (EEfRT hard task choice and EEfRT reward sensitivity). Gene-set analysis revealed significant associations between our quantitative GWAS for EEfRT hard task choice and gene-sets involving dopamine receptor signaling, a known essential reward-processing pathway. Significant associations were also found in gene-sets involved with limbic system and forebrain development, as well as a gene-set comprised of proteins known to be involved in the brain’s response to cocaine. In addition, PRS generated from EEfRT hard task choice were significant predictors of parent-reported levels of psychopathology in our child participants; specifically, the PRS predicted elevated levels of symptomatology on scales that previous research has associated with anxiety, depressive disorders, schizophrenia, and autism spectrum
disorders. These findings provide support for the concept of a genetic basis for effort-based reward behavior that is associated with a wide variety of diagnostic forms of psychopathology.

Results from our study align with associations between reward behavior and psychopathology that have previously been established in the psychiatric research literature. This is a vital first step in demonstrating the feasibility of applying the RDoC-based approach to genetic studies. As RDoC is intended to be a constantly evolving research framework, it is also necessary to establish which components of the RDoC vision are scientifically sound, and which portions need revision. To that end, our study design successfully applied the RDoC research framework to GWAS, a field dominated by traditional disease/disorder-based approaches. Identifying genetic loci associated with phenotypic measures of effort-based reward behavior provides validation of the construct and lays important groundwork for further study of reward and psychopathology, especially in an RDoC-based context.

Our study faced limitations based on the smaller size of our participant population, so it will be of interest to determine if the associations of reward behavior with the PRS and with specific loci identified here replicate in a larger sample, and whether other RDoC-endorsed quantitative measures of reward behavior might also yield significant genetic associations. Another important limitation to consider is that the EEfRT task is different for children than it is for adults, meaning that the outcome measures generated are likely not directly comparable between adults and children. Given that familiality is a key feature of many forms of psychopathology, it may be important to include recommendations for validated, comparable measures for both adult and child populations in future revisions to the RDoC research framework.
Overall, quantitative measures of effort-based reward behavior were found to be linked to specific genetic variants, and polygenic risk scores derived from these quantitative measures were significantly associated with measures of psychopathology. These findings represent an important first step in application of the RDoC framework towards the study of reward behavior genetics and psychopathology. We hope that this work paves the way for continued research into the understudied PVS domain, including other RDoC subconstructs of reward that were not the subject of this current study, and towards the larger goal of reinstating genes of interest within the RDoC matrix backed by robust empirical evidence of association.
Appendix Chapter 4

Supplementary Table 4.1. Participant Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Parents (N = 1270)</th>
<th>Children (N = 1536)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean +/- SD)</td>
<td>37.4 years ± 6.9</td>
<td>9.0 years ± 3.1</td>
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<tr>
<td>Sex (% female)</td>
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<tr>
<td>Race (% white)</td>
<td>68%</td>
<td>55%</td>
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<td>(% black)</td>
<td>21%</td>
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</tr>
<tr>
<td>(% two or more races)</td>
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<td>14%</td>
</tr>
<tr>
<td>(% other)</td>
<td>7%</td>
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<tr>
<td>Ethnicity (% Hispanic)</td>
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<tr>
<td>Psychiatric (% psychiatric history)</td>
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<td>Education (% less than high school)</td>
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<td>(% high school diploma)</td>
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<td>(% some college/post-secondary degree)</td>
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<tr>
<td>(% bachelor’s degree)</td>
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<tr>
<td>(% master’s/doctoral/professional degree)</td>
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<td>Marital Status (% married)</td>
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<td>(% divorced/separated/widowed)</td>
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<td>Income (% &lt; $10,000)</td>
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<tr>
<td>(% $10,001 – 20,000)</td>
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<td>(% $20,001 – 30,000)</td>
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**Supplementary Table 4.2. Significant Results for Adult EEfRT Hard Task Choice**

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<th>P-Value</th>
<th>Total # SNPs in Clump</th>
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**Supplementary Table 4.3. Significant Results for Adult EEfRT Reward Sensitivity**

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<th>P-Value</th>
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Bibliography Chapter 4

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Chapter 5: Summary and Impact

It has been more than a decade since the launch of the RDoC project by the NIMH in 2009. This strategic initiative was designed to address the scientific concern that the field had defined psychiatric illness via syndromes of clinically observed diagnostic criteria that were not well connected with neural and psychological mechanisms. The project aimed to instead consider psychopathology in terms of dysfunction and dysregulation in fundamental elements of human psychology, by integrating multiple levels of information, including genomics, circuits, physiology, and behavior. Under this framework, basic neuroscience and behavioral science research can establish the basic dimensions of functioning and build upwards towards the full range of human behavior, ultimately informing a classification system with more homogenous groupings for psychopathology and pathophysiology (Pacheco et al., 2022).

The current overarching model of psychiatric classification (DSM/ICD) views mental disorders as largely discrete entities that can be characterized by distinctive signs, symptoms, and natural histories (Lilienfeld & Treadway, 2016). Although this model has undoubtedly been instrumental in scientific progress and treatment development over the last half century, there has been an accumulation of unresolved anomalies that, despite multiple large-scale revisions, continue to plague both research and clinical practice (Lilienfeld, 2014). Phenotypic heterogeneity within some diagnostic categories borders on absurdity; for example, there are 636,120 ways in the DSM-5 to meet the diagnostic criteria for PTSD, and it is even possible for two people to meet the DSM-5 threshold for obsessive-compulsive disorder without sharing any diagnostic criteria (Galatzer-Levy & Bryant, 2013). Comorbidity is another rampant issue within this system, with statistical analyses demonstrating that for multiple disorders, a majority of individuals meet the diagnostic criteria for at least one other DSM-defined disorder (Craighead,
Miklowitz, & Craighead, 2013). Most importantly, perhaps, psychiatry has not seen the same reductions in morbidity or mortality as seen in other disciplines of medicine, and there exists a stark lack of specificity among many of the treatment options currently available for major mental disorders (T. R. Insel, 2009). The dimensional approach of RDoC is intended to address these challenges. In contrast to the DSM/ICD, the RDoC approach is explicitly transdiagnostic as it seeks to identify markers of dysfunctional psychobiological circuitry that transcend multiple traditional disorder categories. It places a strong translational emphasis on application of the basic sciences of brain systems and behavior to understanding psychiatric disorders (Lilienfeld & Treadway, 2016). Additionally, the dimensional structure of RDoC is a response to evidence indicating that activity of most brain circuits is continuously distributed, with little to no clear-cut boundaries between normality and abnormality (Cuthbert & Insel, 2013).

Since its inception, the RDoC framework has contributed to a significant amount of funding, research efforts, and publications, although the distribution of those among the six domains has not been equal. This trend is also seen within domains themselves; while Positive Valence Systems is among the top three domains in terms of publications, a majority of these have focused on the constructs of ‘reward responsiveness’ and ‘reward learning’ (Carcone & Ruocco, 2017). Against this backdrop, we chose to focus on the lesser studied construct of ‘effort’ within the PVS domain. ‘Effort’, which specifically refers to the modulating effect of the physical or cognitive costs on reward evaluation, is an elemental unit of human behavior that has been previously associated with multiple forms of psychopathology.

The current dissertation presented three studies that responded to the newly formed RDoC project’s need for validation. Study 1 utilized initial behavioral task and self-report analyses to establish an empirical basis for the ‘effort’ construct’s associations with
psychopathology and developmental stability. It sought to determine whether ‘effort’ as defined in the RDoC system would demonstrate relationships to psychopathology with the same characterization as had been observed in previous DSM-oriented studies of analogous concepts such as motivation. Study 2 was a continued effort towards validation in assessing the ‘effort’ construct’s reliability, coherence, and divergent validity in an expanded participant sample. It also responded to the surprising lack of developmental stability found in Study 1 through a more comprehensive comparison of behavioral measures of ‘effort’ within families. Finally, Study 3 used genome-wide analyses to establish and characterize the effects of ‘effort’ genes in children and adult psychopathology.

Study 1

It is well established in the literature that effort-based decision making is impacted in multiple traditional psychiatric disorders. Previous research has observed consistent abnormal increases in effort allocation in disorders such as anxiety and ASDs, and abnormal decreases in effort allocation is MDD and schizophrenia (Barch et al., 2014; Berchio et al., 2019; Damiano et al., 2012; Treadway et al., 2012). However, the bulk of research in this area has been conducted on adult participants, rather than children, and there are no RDoC-designed studies investigating the relationship between the ‘effort’ construct and psychopathology. Although the findings in adults indicate that measures of ‘effort’ could be useful predictors of psychiatric disorders, it is not clear if ‘effort’ relates more broadly to psychopathology or if any associations with psychopathology are consistent across age and sex.

To address these gaps in the literature and establish the RDoC construct of ‘effort’ as relevant for psychiatric research, Study 1 utilized a behavioral task and several self-report measures to examine ‘effort’ as a correlate of psychopathology in children and adults. Given that
this study was the first to investigate ‘effort’ and psychopathology under the RDoC framework, our hypotheses were based on previous non-RDoC literature. We hypothesized that ‘effort’ would be a significant correlate of multiple dimensions of psychopathology, and that there would be sex-related differences in the characterization of that linkage. In concordance with these hypotheses, ‘effort’ was found to be significantly associated with anxiety and thought problems in children, and with substance abuse in adults. For these associations, males who exhibited low effort allocation and/or reward sensitivity also reported significantly higher severity of psychopathology problems relative to female participants with low effort allocation and/or reward sensitivity. Study 1 also investigated the cross-generational and familial continuity of the ‘effort’ construct by comparing measures between parents and their children and between siblings. We hypothesized based on trends observed in the literature that ‘effort’ would be predictive of similar domains of psychopathology between adults and children and that it would be significantly correlated both among siblings and between parents and their children. To our surprise, the findings of Study 1 did not match these hypotheses; ‘effort’ associated with measures of psychopathology that were different between adults and children, and measures of ‘effort’ only significantly correlated between siblings, but not parents and their children (Nguyen et al., 2019).

Findings from Study 1 establish ‘effort’ as a relevant construct for the study of psychopathology under the RDoC framework. Observations regarding low effort allocation, low reward sensitivity, and their associations with anxiety, thought problems, and substance abuse demonstrate that these components of reward processing deficits may be important therapeutic targets to address. Although the relationships between ‘effort’ and multiple areas of psychopathology were significant and varied by sex, the small magnitude of these correlations
and the large number of tests of association that were negative indicate that ‘effort’ dysfunction is more likely a contributing factor rather than a driving force for psychopathology in children and adults. The surprising lack of parent-child correlations for ‘effort’ measures suggests that perhaps the child and adult assessments for ‘effort’ do not gauge the same constructs, or that ‘effort’ and its correlates change as a child moves through stages of development. Ultimately, this study laid the groundwork for future RDoC-based study of effort-based decision making and psychopathology in both children and adults.

**Study 2**

Study 1 demonstrated a successful first foray into RDoC-based investigation of effort and psychopathology in families, with findings that provided support in favor of the feasibility of the RDoC approach. Study 2 continues this endeavor to further investigate the cross-generational stability of ‘effort’ in families, as the lack of these correlations found in the first study contrasted with trends observed in the literature (Belleau et al., 2021; Kamarajan et al., 2017; Martin-Soelch et al., 2021; Singh et al., 2014). And as Study 1 represented the first RDoC-based study of ‘effort’ and was also the first study to apply the EEfRT behavioral paradigm in children, it was also important to assess the replicability of associations with psychopathology in an expanded participant population. Given that RDoC is designed to be a continually evolving and iterative research framework in response to research evidence, the next logical step in empirical validation of ‘effort’ was to assess its divergent validity from other PVS constructs, especially since the PVS domain had undergone structural reorganization after Study 1 was conducted. To this end, Study 2 compared measures of ‘effort’ with multiple measures of ‘reward responsiveness’ and ‘reward learning’ via multitrait multimethod matrices to test for divergent validity.
‘Effort’ was found to have divergent validity from other PVS constructs of reward behavior, lending further empirical evidence in support of the RDoC framework. To our knowledge, these findings are the first evidence-based assessment of divergent validity among PVS constructs. In the expanded participant population, Study 2 still found the same associations with psychopathology among children and adults as reported in Study 1, with the same sex-specific characterization. These findings indicate that abnormalities in effort-based decision making may be a reliable predictor of psychopathology, and the moderating effects of sex on those relationships serves to underscore the importance of incorporating sex-specificity in reward behavior research and treatment development. Most importantly Study 2 utilized multiple methods and approaches to assessing the cross-generational stability of ‘effort’ in parents and children, confirming the initial findings of Study 1. Correlations between siblings for ‘effort’ measures remained significant, while correlations between either parent and their children for ‘effort’ were not. Given that existing literature has demonstrated familial continuity for the types of psychopathologies most associated with impaired ‘effort’, these findings raised important implications for future research on ‘effort’ and for future revisions and updates to the RDoC framework. In particular, many of the reward behavioral measurement tasks endorsed by the NIMH for the study of PVS constructs were developed, validated in, and intended for adults, including EEfRT. Because of this, it is not clear whether applying such tasks in both adults and children is fully equivalent. In psychiatry, the early detection of and early interventions for the development of psychiatric disorders is an underdeveloped and poorly understood area (Lee, Kim, & Kwon, 2019; Lieberman, Small, & Girgis, 2019; Zhang et al., 2019). As such, it may be important for RDoC-endorsed methods of study to be well-established in children or for there to be child-validated alternatives listed within the matrix. Additionally, although it is not a
component of the RDoC matrix, one of the stated RDoC goals is to understand developmental trajectories across various phases of the life span (Cuthbert, 2014). The current iteration of the RDoC framework includes no explicit guidelines on this component, preferring to leave study design and specific research direction up to investigators’ discretion. However, it may be necessary to incorporate delineations for phases of development across the lifespan within which RDoC constructs demonstrate consistency, especially if the characterization of these constructs change over time such that comparison across phases is not logical. Our findings support longitudinal research as an essential component to a revision of this nature.

*Study 3*

The third and final study in this dissertation builds upon the findings from Study 1 and Study 2 on associations between behavioral measures of ‘effort’ and psychopathology, by seeking to understand the genetic basis of ‘effort’ in children and adults. Prior to this study, the NIMH had removed specific reference within the RDoC matrix to any specific genes, explicitly calling for genome-wide association studies of RDoC constructs to provide empirical evidence for genes of interest. Study 3 is a direct response to this call and seeks to round out our understanding and characterization of the ‘effort’ construct. Existing literature on the larger picture of reward behavior genetics and psychopathology has found candidate genes linked to performance on a delay-based decision-making task. Linkage disequilibrium score regression found positive genetic correlations between delay discounting and ADHD and MDD, but negative genetic correlations with SCZ (Sanchez-Roige et al., 2018). However, no specific research has been conducted to date on the genetics of effort-based decision making and psychopathology. Additionally, the usage of disorder-agnostic, quantitative measures of psychological function rather than diagnostic classification in genome-wide association analyses
is a relatively rare, but more RDoC-aligned approach (Sanchez-Roige et al., 2018). Study 3 sought to apply this novel approach to this understudied area of psychiatric genetic research.

Genome-wide association analyses found genetic loci on three separate chromosomes that were significantly associated with quantitative measures of effort-based reward behavior, indicating that ‘effort’ has a concrete genetic contribution. Furthermore, gene-set enrichment analysis yielded significant associations between our quantitative genomic data and multiple gene sets involved in reward processing-related pathways, including dopamine receptor signaling, limbic system and forebrain development, and biological response to cocaine. Study 3 also demonstrated that PRS generated from a quantitative measure of ‘effort’ was a significant predictor of parent-reported levels of psychopathology in child participants. The PRS predicted elevated levels of symptomatology on scales that have been associated with disorders such as anxiety, depression, schizophrenia, and autism in previous research. In totality, these findings provide empirical support for the concept of a genetic contribution to ‘effort’ and its relationship to a wide variety of psychiatric diagnoses. Furthermore, this study successfully applied a RDoC-based design to a field dominated by traditional disease/disorder-based approaches and strengthens the validity of ‘effort’ as an RDoC construct relevant to psychopathology.

Integration of Findings

The three studies that make up this dissertation independently and collaboratively contribute to our understanding of the behavioral and genetic relationship between effort-based decision making and broad psychopathology. They represent and demonstrate a focused application of the RDoC research framework to a unit of human psychological function to advance our knowledge of psychiatric reward behavior and provide critical feedback and evaluation of the RDoC system. Across these three studies, ‘effort’ was assessed with respect to
its reliability, coherence, divergent validity, developmental stability, associations with psychopathology, and genetic familiality, none of which had been assessed before.

Behavioral measures of ‘effort’ in children were significantly associated with and predictive for anxiety and thought problems, and increased impairments in effort allocation among males are associated with greater problem severity relative to females. In adults, behavioral measures of ‘effort’ are significantly associated with and predictive for substance abuse problems, with increased impairments in effort allocation among male adults being associated with greater problem severity relative to females. ‘Effort’, in comparison to other RDoC constructs and subconstructs of reward behavior, has divergent validity. However, ‘effort’ does not appear to be developmentally stable over time, as adult measures did not correlate with child measures; only siblings’ measures of ‘effort’ correlated significantly.

‘Effort’ was found to have concrete genetic contributors in adults, with genome-wide significant polymorphisms across three separate chromosomes. Gene sets from biological pathways involved with reward processing in adults were also associated with quantitative behavioral measures of ‘effort’, indicating that phenotypic aberrations in effort-based decision making are likely to have an underlying biological mechanism. Lastly, polygenic risk score analyses demonstrated that the contribution of abnormalities in ‘effort’ to psychiatric phenotypes in children is based on the combined effect of many smaller variations in genes. Although these results provide evidence indicating that ‘effort’ function may have concrete biological roots influenced by genetics, there are still many too many layers between genes and behavioral phenotypes to draw direct causal relationships. Further research specifically designed to explore and characterize the details of these initial results is warranted to determine the exact nature of how these genetic variants contribute to aberrant function. However, these findings illustrate the
breadth and the complexity of the relationship between reward behavior and psychopathology, which ultimately supports the utility and necessity of the RDoC approach to the further progression of psychiatric medicine and psychiatric research.

**Research Implications**

Findings from this dissertation have demonstrated the feasibility and validity of the RDoC approach to the study of psychopathology. Although the concepts and constructs outlined within the RDoC PVS domain are not new in the field of psychiatry, there is need for empirical validation and investigation of those other (non- ‘effort’) constructs to continue to advance the RDoC project and our understanding of human psychological function. While previous research relating specific disorders such as anxiety, depression, and schizophrenia to aberrations in reward behavior have been conducted, a disorder-agnostic RDoC aligned investigation of ‘reward learning’ and ‘reward responsiveness’ had yet to be pursued. Characterizing these constructs’ relationship with broad psychopathology in addition to specific disorders is critical to building up a thorough understanding of the etiology of psychiatric illness. Additionally, these constructs have the potential to be incredibly useful in informing the future development of more internally homogenous diagnostic categories. For instance, existing literature has observed major comorbidity between anxiety and depressive disorders, presenting barriers to treatment and leading to worse psychiatric outcomes (Aina & Susman, 2006). While these types of disorders under their current DSM/ICD definitions have a significant degree of overlap, anxiety disorders are more consistently associated with higher than normal effort allocation, whereas depressive disorders are more consistently associated with lower than normal effort allocation (Berchio et al., 2019; Treadway et al., 2012). Future diagnostic categories developed from quantifiable behavioral profiles based on these types of trends may be more internally homogenous and
representative of the underlying biology and may therefore be more conducive to effective
treatment development. The present dissertation outlines both behavioral and genetic
investigations that future research could conduct on other PVS constructs and other domains of
RDoC that would be invaluable towards this development.

While the behavioral and genetic investigations within the present dissertation examine
the ‘effort’ construct in the context of psychopathology, it may be necessary to first direct future
research towards a specific focus on establishing normative patterns and values for measures of
‘effort’ in both children and adults. The RDoC framework itself has a stated goal of
quantitatively characterizing the range of normal function for each construct (Cuthbert, 2015).
As of this writing, although the EEfRT is still the only NIMH-endorsed paradigm for the study
of the ‘effort’ construct, to our knowledge, research establishing norms for EEfRT in adults and
children does not yet exist. Without this information, it is difficult to interpret the degree of
pathology represented by EEfRT measures. Ideally, such norms should be established for all the
paradigms endorsed by the NIMH for the study of RDoC constructs. Given that the prevailing
view in recent years of psychopathology is dimensional, with varying degrees of departure from
the normal range, RDoC constructs can then be utilized to define cutoff points for mild,
moderate, or severe levels of disorder (Cuthbert, 2005; Van Os, 2013). Furthermore, once norms
and cutoff points are determined, the next logical step would be to apply construct paradigms in
a large population to assess trends and patterns and assemble these to build profiles of reward
behavior. Profile definitions can be tested in psychopathologic populations to investigate their
predictive capability as well as to assist in improving diagnostic classifications and definitions. It
is possible that psychiatric disorder heterogeneity under current diagnostic definitions can be
addressed via these profiles of RDoC constructs.
Clinical Implications

Findings from this dissertation consistently demonstrated sex-specific differences in the relationship between effort-based decision making and psychopathology. Male participants observed to have decreased effort allocation in behavioral paradigms were also observed to have relatively high severity of psychopathology problems on self-report scales, indicating that measures of ‘effort’ may be predictive in males specifically for worse psychiatric outcomes. This is important both from the perspective of diagnosis as well as intervention. Sex differences have been observed across a wide variety of psychiatric disorders, including differences in brain structure, function, stress responsivity, exposure to reproductive hormones, social expectations and experiences (Altemus et al., 2014). Certain mental health disorders featuring abnormal reward processing also display disproportionate incidence rates between the sexes, such as the higher rates of depression in women, or the higher rates of substance abuse, autism, or ADHD in men (R. K. McHugh, Votaw, Sugarman, & Greenfield, 2018; Rubinow & Schmidt, 2019).

However, it is important to note that our understanding of which sex differences are specifically relevant to psychiatric illness is still evolving. Although ADHD is more commonly diagnosed in males than females, recent findings have indicated that this may be in part due to sex bias in the diagnostic process, where sex differences in the phenotypic expression of ADHD are often proposed as the source of the greater rates in males (Mowlem et al., 2019). With this example in mind, it is clear that sex differences in human psychological functions are important aspects of psychopathology to study as they can better inform our diagnostic processes. RDoC constructs such as ‘effort’ are an ideal foundation to assess these sex differences at an elemental level. Our findings suggest that research on identifying biomarkers or other early indicators of
psychopathology in males may benefit from focus towards measures of impaired reward behavior.

With respect to interventions, investigating and understanding sex differences may be even more critical than in diagnosis. Biological differences between men and women, including factors such as brain structure/function and exposure to reproductive hormones, have significant implications for response for existing treatments and targets for developing treatments (LeGates, Kvarta, & Thompson, 2019). A growing area of focus in advancing our understanding of the pathophysiology of depression and anti-depressant response is sex-specific changes in synaptic strength and synaptic transmission, especially in reward-related brain areas such as the hippocampus, prefrontal cortex, and nucleus accumbens (Galea et al., 1997; Garrett & Wellman, 2009; Wissman, May, & Woolley, 2012). In addition to these structural factors, there are sex-specific physiologic differences in pharmacokinetics of drug absorption and metabolism (Bigos, Pollock, Stankevich, & Bies, 2009). These are key indicators that reinforce the importance of incorporating analyses of sex differences, especially with regards to psychiatric illness and psychological function. Lastly, of particular additional interest is recent research assessing sex differences in compliance and adherence to antidepressants, where investigators found average adherence for older males (age 50-70) was significantly lower than females at that same age range (Krivoy et al., 2015). This trend is particularly relevant in the context of the use of incentives to increase medication to adherence, where studies have observed that for some medications, incentives increased adherence by a mean of 20 percentage points (DeFulio & Silverman, 2012). These findings in combination suggest that it is possible that males with psychiatric disorders where reward behavior is adversely affected may have poorer outcomes due to lack of medication adherence which is refractory to the use of incentives. In conjunction with
our findings, this could indicate that development and administration of treatments that specifically target reward behavior deficits and ‘effort’ abnormalities may be much more important for male patients suffering from psychiatric illness.

**RDoC Implications**

The RDoC research framework was designed from its inception to be updated over time to reflect and keep up with findings in the literature. Significant changes to the RDoC matrix have already been made and have been discussed previously within this dissertation, including the removal of specific genes recommended for study and the major reorganization of the PVS domain (National Institute of Mental Health, 2018). Our studies responded to these changes, assessing aspects of the ‘effort’ construct before and after the reorganization, as well as identifying genomic variants associated with ‘effort’ through genome-wide analyses. In addition to these responses to direct changes within the RDoC system, our findings also raised important questions regarding developmental continuity and developmental trajectories of RDoC constructs. The lack of parent-child correlations for measures of ‘effort’ suggested that either the construct changes over time as individuals move through developmental phases, or that the NIMH-endorsed EEfRT paradigm does not measure the same construct in children as in adults. Although investigations of familial correlations for other RDoC constructs may help provide more information and context regarding this issue, revisions to the RDoC matrix to provide guidance for the study of RDoC constructs in children seems particularly salient. The study of early signs and symptoms of psychiatric illness in children may be critical to advancing clinical capabilities for early detection and early interventions. Further progress in this area is a high priority given the evidence that disorders with earlier onsets can be more severe and have more persistent courses than disorders with later onsets (De Girolamo, Dagani, Purcell, Cocchi, &
McGorry, 2012). Additionally, there is a growing body of work in the field of psychiatric research demonstrating that early childhood expressions of psychopathology are predictive for impairments in adolescence and later for a wide variety of mental health disorders (Finsaas et al., 2020; O’Neill, Rajendran, Mahbubani, & Halperin, 2017; Scott et al., 2021). Altogether these findings serve to further highlight the necessity of a more formalized RDoC framework for future studies in children.

Along these same lines, our findings also support and underscore the need for longitudinal study of human psychological function. Although future research is necessary to provide the empirical basis for detailed revisions and additions to the RDoC framework, the current iteration of RDoC provides no specific guidelines or recommendations for studies of constructs over time. Using ‘effort’ as an example, psychiatric literature has demonstrated that in children, developmental shifts occur in decision-making during adolescence (Hartley & Somerville, 2015). Risk-taking behavior is increased in adolescents, which is often attributed to extensive structural and functional brain development occurring at that time. And although risk-taking encompasses more than reward-based behavior, a previous study found evidence for increased limbic responses to reward stimuli that peaks in mid-adolescence, indicating that reward behavior is an affected component of adolescent development (Crone & Dahl, 2012). While our findings provide a basis of knowledge regarding ‘effort’ in pre-adolescent children, an important next step would be continued study of ‘effort’ in adolescents and young adults. Future longitudinal research characterizing the stability or instability of this and other constructs over time may eventually evolve the RDoC matrix such that construct definitions, features, and recommended study methodologies may be subdivided by developmental phases. This detailed
level of understanding would be invaluable for not only guiding research, but also development of treatments/interventions and specific assessments of their efficacy across the lifespan.

Conclusions

This dissertation provided a critical first foray into an RDoC-based approach of the study of effort-based decision making and psychopathology in children and adults. Multiple behavioral and genetic analytical methodologies were employed to investigate ‘effort’ construct reliability, coherence, divergent validity, developmental stability, associations with psychopathology, and familiality. These three studies addressed important gaps in the literature concerning the application of RDoC towards human reward processing and psychopathology, as well as specific characterizations of these relationships in children versus adults and between sexes. It is my hope that the findings and discussion points raised within this dissertation contribute towards further improvement of the RDoC system and inform future RDoC-based research on human psychiatric function.
Bibliography Chapter 5


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