EXECUTIVE FUNCTION IN HUNTINGTON'S DISEASE AND MAJOR DEPRESSIVE DISORDER: MODERATORS AND ASSOCIATIONS WITH EMOTION REGULATION

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To my parents, Marni and Dan, for fostering my love of learning and providing me with the tools to access an extraordinary education.

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1 INTRODUCTION

1.1 Overview

A primary focus in the field of clinical neuropsychology is the identification and monitoring of impairments in cognitive and executive functioning in psychiatric and medically ill populations. Elucidating neuropsychological profiles that are unique to and shared across certain populations is important for improving our understanding of brain–behavior relationships and either supporting or challenging existing diagnostic boundaries. In this paper, I will discuss executive functioning impairments in two overlapping but distinct neuropsychiatric disorders: major depressive disorder and Huntington's disease. While much previous research has documented executive functioning impairments in these two populations, research to date has been siloed and has typically used different assessment batteries selected for each disorder. The analyses described in this paper seek to provide clearer comparisons between the two disease groups by using the same measures of executive functioning. I will examine both within- and between-group differences in executive functioning, and then explore associations between domains of executive functioning and emotion regulation using samples from each population.

1.2 Executive Function (EF)

Executive function (EF) describes a set of higher-order cognitive processes that coordinate top-down control of thoughts, emotions, and behaviors (for reviews, see Diamond, 2013; Zelazo, 2020). EF skills are necessary for many aspects of cognitive, social, and adaptive functioning, including learning, regulating behavior, and participating in complex social interactions (Moriguchi, 2014; Zelazo, 2015; Zelazo & Carlson, 2012). In addition, EFs are used to carry out cognitive coping and emotion regulation strategies that help individuals flexibly adapt to changing environments and stressors (Morris et al., 2015; Oh & Yang, 2022). Individual differences in EF predict academic achievement (Best et al., 2011; Daucourt et al., 2018; Dekker et al., 2017; Mulder et al., 2017; Ribner

et al., 2017; Von Suchodoletz et al., 2017), engagement in physical activity and other healthy behaviors (Daly et al., 2015; Hall et al., 2008), obesity (Reinert et al., 2013), occupational functioning (Barkley & Murphy, 2010; Evans et al., 2013; Koene et al., 2022), quality of life (Brown & Landgraf, 2010; Cotrena et al., 2016), and life satisfaction (Oh & Yang, 2022; Toh et al., 2020). Further, a wide range of psychiatric and neurological conditions are associated with compromised EF, and it has been suggested that EF difficulties may be a useful transdiagnostic indicator of developmental risk for psychopathology (Marije Boonstra et al., 2005; Moran, 2016; Scott et al., 2015; Snyder, 2013; Zelazo, 2020).

EF skills are subserved by neural circuits in several brain areas, including the prefrontal cortex, parietal cortex, and other cortical and subcortical brain regions (Niendam et al., 2012). Behaviorally, EFs are typically measured as three core functions: inhibitory control, working memory, and shifting (e.g., Miyake & Friedman, 2012). Inhibitory control describes the skill of maintaining attention on the task at hand while filtering out distractions and suppressing impulsive behaviors. Working memory (also referred to as updating) describes the skill of holding and manipulating information in mind (e.g., solving simple math problems or putting a random string of numbers in descending order). Shifting (also referred to as cognitive flexibility or task switching) involves flexibly adjusting to new task demands, rules, or priorities (e.g., matching sets of items by color and then by shape or considering a situation from multiple points of view; Diamond, 2013).

1.2.1 Contemporary Models of EF

While most models of EF support the presence of three core functions, the details and hierarchical structure of this system remain the subject of ongoing research. For example, the frequently-cited unity and diversity model of executive functions (Friedman & Miyake, 2017; Miyake & Friedman, 2012) was identified using confirmatory factor analyses to examine the associations among latent EF variables. Results supported a bifactor model–in which inhibitory control is

subsumed by a "common EF" factor and working memory and shifting are distinct factors–as the best fitting model (Miyake & Friedman, 2012). The authors interpret the subsumption of inhibitory control by the common EF factor in this model as suggesting a potential overarching role of inhibitory control necessary for task coordination (e.g., maintenance of goals and implementation). A recent systematic review and re-analysis of 17 studies applying confirmatory factor analysis to EF measurement across the lifespan found that this unity and diversity framework was the most frequently accepted and selected model of EF among studies with adult samples (Karr et al., 2018).

Other models (e.g., Baddeley, 2012) describe working memory as the core EF. For example, Baddeley's classic (1974) model proposes that a "central executive" coordinates top-down control processes necessary to sustain working memory (Baddeley & Hitch, 1974). In Baddeley's model, working memory is the primary component of EF, and the process of holding and manipulating information in working memory is supported by inhibitory control and switching processes. Baddeley theorizes that the central executive would need to be able to serve several functions in the maintenance of goal-directed behavior: focus attention, divide attention between multiple stimulus streams, and switch between tasks. Thus, he suggests that inhibitory control and switching would be subsumed by this common factor but does not describe distinct capacities responsible for inhibitory control or switching. Other theories that conceptualize working memory as the primary EF include Cowan's Embedded Process Theory (Cowan et al., 2005) and individual difference-based theories (e.g., Engle et al., 1999; Engle & Kane, 2003), which both contend with the specific capacity of working memory and the importance of inhibitory processes for filtering out distractions that may disrupt working memory.

1.3 Effects of lifespan development and neuropsychiatric conditions on EF

1.3.1 Lifespan development of EF

Because EFs emerge in infancy and continue to develop through early, middle, and later adulthood, it is important to consider EF from a lifespan developmental perspective. In general, improvements in EF abilities coincide with the protracted development of prefrontal brain regions, with performance on EF measures reaching approximate adult levels at approximately twelve years of age but continuing to become more refined across adolescence and into young adulthood (Ferguson et al., 2021; Zelazo & Müller, 2002). EF abilities typically begin to decline in the third to fourth decade of life (Ferguson et al., 2021), with emerging evidence suggesting that this prototypical decline is strongly related to decreased functional connectivity within brain regions that becomes more pronounced across younger to older adulthood (Fjell et al., 2016; Grady et al., 2016).

Importantly, declines in EF may be hastened among individuals with neurological and psychiatric conditions that impact the structures and functional networks that facilitate EF (Snyder et al., 2015; Zelazo, 2020). Understanding the associations of these deficits with psychiatric symptoms and patients' ability to engage in adaptive behaviors is especially important because EF dysfunction negatively impacts the ability to engage in independent living skills (e.g., Johnson et al., 2007; Marshall et al., 2011) and accelerates physical decline (e.g., Gross et al., 2016). Cognitive and EF complaints are also associated with increased psychological distress (e.g., Nicol et al., 2019; Pranckeviciene et al., 2017; Pullens et al., 2010).

1.3.2 EF in physical and neuropsychiatric conditions

Many physical and mental health problems are associated with compromised EF. Impairments in EF have been documented in several chronic physical health conditions in adult populations, including type 2 diabetes (Sadanand et al., 2016), breast cancer (Yao et al., 2017), and hypertension (Moraes et al., 2019). Deficits in EF are common in a wide range of psychiatric conditions, including anxiety (Moran, 2016), depression (Rock et al., 2014; Snyder, 2013; Yang et al., 2017), eating disorders (e.g., Miranda-Olivos et al., 2021), and posttraumatic stress disorder (Scott et

al., 2015). EF systems are also among the most vulnerable to decline in neurodegenerative diseases, including Huntington's disease (HD; Ciriegio et al., 2022; Dumas, 2013).

EF deficits are likely to arise from conditions that affect the prefrontal lobes, and cortico-striatal or cerebro-cerebellar circuitry (Koziol & Budding, 2009). Because EF is so frequently impaired across the diagnostic categories defined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5-TR; American Psychiatric Association, 2022), EF measures are not typically sensitive enough to differentiate between the conditions in the DSM without behavioral observations and additional clinical information on affective symptoms and functional impairment (Koziol & Budding, 2009). That is, EF deficits may be transdiagnostic. However, as our understanding of the neural correlates of various DSM disorders increases, so does interest in using neuropsychological tools to better characterize behavioral phenotypes and describe brain–behavior relationships that may underlie symptoms. One way to broaden our understanding of the phenotypic expression of brain–behavior relationships is to examine how EF impairments differ between groups from different diagnostic categories and to explore how variations in EF are associated with functional outcomes of interest, including coping/emotion regulation and psychological well-being.

One of the guiding frameworks for understanding neuropsychiatric disorders and commonalities and differences in their presentations comes from the National Institute of Mental Health's Research Domain Criteria (RDoC) initiative (Cuthbert, 2015, 2022; Cuthbert & Insel, 2013; Insel et al., 2010). The focus of RDoC is on understanding the underlying substrates that define neuropsychiatric disorders, and to empirically derive and conceptualize fundamental dimensions that are distinct from the phenotypic symptoms listed as diagnostic criteria. RDoC's goals center on improving our understanding of psychological functioning by better characterizing underlying biological processes and neural circuitry. RDoC proposes that, in order to accelerate the translation of research to improve clinical practice, it is necessary to reconceptualize our diagnostic systems.

Beyond knowing whether a patient meets diagnostic criteria based on observable symptoms for a given disorder, an increased understanding of brain-behavior relationships allows clinicians to conceptualize symptoms at multiple levels (Cuthbert, 2015, 2022). The RDoC domain of cognitive systems encompasses aspects of EF, including working memory, attentional control, and cognitive complexity. An important next step in advancing RDoC involves making direct comparisons of DMS-5-TR disorders to identify similarities and differences on the RDoC dimensions.

Two conditions described in the DSM-5-TR with known EF impairments are Huntington's disease (HD), an rare, inherited neurodegenerative disease with psychiatric features, and major depressive disorder (MDD), a psychiatric disorder and the leading cause of disability worldwide (Friedrich, 2017). Like many conditions in the DSM, these conditions share substantial overlap in that they are both associated with a cluster of affective, behavioral, and cognitive phenotypic symptoms and are characterized both by social withdrawal and significant functional impairment. In addition, depression symptoms are common among individuals with HD. Notably, while EF deficits are common challenges associated with both diagnoses, neither disorder is diagnosed solely based on EF impairments.

In addition to these similarities between HD and MDD, there are marked differences between these two disorders that set the stage for compelling comparisons. First, while both HD and depression run in families, they have different genetic loads. HD is an autosomal dominant inherited condition with a clear genetic marker (i.e., offspring of patients with HD have a 50% chance of inheriting the fully-penetrant, mutant huntingtin gene that causes HD). In contrast, there is also clear evidence for intergenerational transmission of depression via *polygenetic* (e.g., 5HTTLPR, Val66Met) and environmental mechanisms (Goodman, 2020; Goodman & Gotlib, 1999; Lohoff, 2010).

Second, neural circuitry is impacted through different mechanisms, which may underlie different cognitive and behavioral phenotypes. A recent review of neuroimaging studies indicated that individuals with MDD demonstrate abnormal functioning in lateral and medial prefrontal areas when they are exerting voluntary control during emotion processing (Rive et al., 2013). Reduced cognitive control in individuals with MDD has also been linked with reduced brain activity in the dorsolateral prefrontal cortex and the dorsal anterior cingulate cortex (Webb et al., 2016), regions that are activated during EF tasks (Niendam et al., 2012). In HD, mutant huntingtin protein specifically targets the basal nuclei, facilitating neurodegenerative processes that result in motor abnormalities and disrupt fronto-striatal circuitry from the bottom up (Duff et al., 2010; Ross & Tabrizi, 2011). Neuropathological features of both disorders are described in more detail in the next section.

Third, the two conditions may impact performance on different EFs to a different extent. Inhibitory control is likely to be the most vulnerable to the neurodegenerative processes inherent to HD because of the effects of mutant huntingtin on the basal nuclei and ventral striatum (Halliday et al., 1998; Vonsattel, 2008). Because rumination and information processing biases are core features of depression, working memory and decreased responsivity to reward may be most at risk in MDD (Gotlib & Joormann, 2010; Proudfit et al., 2015). In turn, these differential impacts on EF may uniquely predict affected individuals' ability to engage in cognitive coping strategies that rely on intact and efficient EF.

As described in a recent review of neurocognitive deficits in children with chronic health conditions (Compas, Jaser, Reeslund, et al., 2017), translational research seeking to improve understanding of neurocognitive deficits and enhance clinical care has likely been hampered by researching individual conditions in isolation. Research has typically been conducted on single disorders (e.g., brain tumor, Jacob et al., 2018; Robinson et al., 2013; leukemia, Buizer et al., 2009;

Chan et al., 2022; Cheung & Krull, 2015; sickle cell disease, Prussien et al., 2020), using a neuropsychological test battery tailored to that disorder. This siloed approach precludes making clear comparisons of performance on EF measures across conditions. Despite a call for more studies that compare neurocognitive functioning in existing groups on a common set of measures (Compas, Jaser, Reeslund, et al., 2017), little work has been done using this model (for exceptions, see Fraley et al., 2023; Taylor Tavares et al., 2007). Using the same "measuring stick" allows researchers to make comparisons between known groups that are unobscured by measurement differences. By including multiple diagnostic groups, it also advances our understanding of fundamental processes within the RDoC framework.

In the present study, I examine two DSM-5-TR disorders, MDD and HD, with distinct phenotypic expressions and with different neural correlates and signatures. I examine EF using a common set of performance-based measures that map onto brain processes known to subserve those functions. In one sense, I would expect profound and pervasive deficits in individuals with neurodegenerative disease (e.g., HD). However, I would also expect deficits in MDD, given that EF is typically implicated but is not seen as hallmark of this disorder. This study is the first to utilize a standard battery to compare these two disorders within the RDoC framework using neuropsychological tools. In doing so, I can better elucidate specific deficits unique to certain disease populations, but also identify areas of challenge that are common across disease groups and may benefit from more general interventions. This provides a model of how future research can use neurocognitive screening tools that are easy to administer and score to enhance our understanding of EF deficits in known and unknown diagnostic groups.

1.4 Major Depressive Disorder: Disease Overview

Major Depressive Disorder (MDD) is one of the most prevalent and burdensome mental health disorders. Between 2013-2016, 8.1% of adults ages 20 and older in the United States

experienced at least one depressive episode (Brody, 2018). Nationally representative surveys of psychiatric disorders (i.e., National Comorbidity Survey; National Comorbidity Survey–Revised) estimate the lifetime prevalence of MDD to be between 16.2-17.1% (approximately 32.6-35.1 million US adults; Kessler, 1993; Kessler et al., 2003). Moreover, longitudinal research utilizing frequent assessments suggests that the lifetime prevalence of MDD may be as high as 40% (Moffitt et al., 2010). MDD is the leading cause of disability worldwide (Friedrich, 2017), exerting substantial functional impacts on individual lives (e.g., role impairment; Evans et al., 2013) and economic impacts at the national level (e.g., workplace costs; Greenberg et al., 2021).

1.4.1 Behavioral and neural correlates of depression

MDD is a mood disorder consisting of one or more depressive episodes characterized by low mood or loss of interest in once-enjoyable activities for a duration of two weeks or longer (American Psychiatric Association, 2022). Additional symptoms are both cognitive (difficulty concentrating or making decisions, disproportionate guilt, thoughts of worthlessness and death) and behavioral (sleep disturbances, appetite changes, psychomotor slowing, low energy; American Psychiatric Association, 2022).

1.4.2 EF in Depression

While MDD manifests differently depending on an individual's combination of presenting symptoms, core elements are dysregulated emotion processing and maintenance of negative affect (Gotlib & Joormann, 2010). MDD is characterized by disruptions in emotion regulation processes, including increased engagement with negative information, which may occur via ruminating on negative information, having difficulty disengaging from negative information, or as a function of impaired cognitive control when processing negative information (Foland-Ross et al., 2013; Gotlib & Joormann, 2010; Joormann et al., 2011).

Biased inhibitory, attentional, and working memory processes play a critical role in sustaining negative affect in depression (Joormann & Tanovic, 2015). There is evidence that individuals with MDD are more likely to pay attention to negative content and elaborate on that content such that it uses more cognitive capacity and reduces available capacity for EFs (Zetsche et al., 2018). A meta-analysis on the association between rumination and core EFs also demonstrated small but significant negative associations between rumination and inhibition and switching (Yang et al., 2017).Thus, both the *content* in working memory and the *processes* through which this information is considered and used are affected individuals with MDD.

EF impairment in MDD has been widely documented both during depressive episodes and subsequently during remission. Several systematic reviews and meta-analyses have explicitly examined cognitive functioning in depression (Ahern & Semkovska, 2017; Nikolin et al., 2021; Rock et al., 2014; Semkovska et al., 2019; Snyder, 2013). A meta-analysis of 113 studies (Snyder, 2013) quantified executive functioning deficits in 3,936 patients with MDD relative to healthy controls, showing large impairments in inhibition and working memory, and moderate impairments in shifting. Patients with MDD also performed significantly more poorly on processing speed measures. Another meta-analysis of 24 studies (compiling results from 784 patients with MDD), found moderate cognitive deficits in executive function, memory, and attention as compared with controls (Rock, Roiser, Riedel, & Blackwell, 2014). Taken together, cognitive signatures of MDD include impairments in processing speed and across the core EF domains of shifting, inhibitory control, and working memory.

The evidence is clear that, despite the episodic nature of depression, cognitive impairments typically persist in patients remitted from depression (Ahern & Semkovska, 2017; Rock et al., 2014; Semkovska et al., 2019). Results from a systematic review and meta-analysis that compiled results from 31 studies examining cognitive functioning during and after a first episode of depression

demonstrated that remission is associated with mild improvements in processing speed and shifting, but that impairments in inhibition persist (Ahern & Semkovska, 2017). Results from a second meta-analysis and systematic review of 252 studies (including 10,126 patients with MDD) indicated that patients with remitted depression significantly underperformed on 73% of cognitive variables relative to matched controls, with the largest deficits observed in working memory and divided attention (Semkovska et al., 2019).

1.5 Huntington's Disease: Disease Overview

Huntington's disease (HD) is a rare neurodegenerative disorder for which there is no existing cure with an estimated prevalence of 5.7 per 100,000 people across Europe, North America, and Australia (Pringsheim et al., 2012). HD is a genetic condition with an autosomal-dominant inheritance pattern, meaning that each offspring of an affected parent has a 50% chance of inheriting the mutant gene that causes HD. The disease is caused by an expanded cytosine-adenine-guanine (CAG) repeat on the huntingtin gene (located on chromosome 4) that codes for a mutant protein; individuals with 36 or more CAG repeats will go on to develop HD (Macdonald, 1993). The disease is characterized by adult-onset neurological, cognitive, and psychiatric symptoms, including chorea, marked EF impairment, and psychiatric disturbance (Dumas, 2013; Ross et al., 2014). Symptoms typically onset in mid-life, between 35 to 50 years of age. However, recent research suggests that human brain tissue from fetuses carrying the mutant huntingtin gene displays clear cellular and cortical abnormalities (Barnat et al., 2020), suggesting a neurodevelopmental component of HD. In line with this emerging evidence that HD seems to affect brain development and function much earlier than mid-life, findings from our research team and others suggest that cognitive symptoms of HD tend to emerge sooner than motor symptoms and are an important marker of disease onset (Pfalzer et al., 2023; Schultz et al., 2021).

1.5.1 Neuropathology of HD

The mutant huntingtin protein affects subcortical and cortical regions. Neuropathologically, the basal nuclei (including the globus pallidus, caudate, and putamen) are implicated (Ross & Tabrizi, 2011). Loss of GABAergic neurons in the caudate has been identified as an early marker of disease in HD, and postmortem examination of brains affected by HD reveals atrophy of frontal lobes and globus pallidus beyond age-related expectations (Tupper, 2011). The primary neurons in the striatum and globus pallidus are GABAergic and thus exert an inhibitory effect on the thalamic and cortical circuits on which they terminate. Thus, the basal nuclei form corticothalamic loops, and inhibitory projections from the basal nuclei to the thalamus and cortical regions modulate activation of this circuitry (Albin et al., 1989; Waldvogel et al., 2014). Left unchecked, these subcortical-cortical-thalamic loops are continuously disinhibited, and dysfunction can result in motor abnormalities, impaired memory formation, attention deficits, diminished inhibitory control, affective symptoms, and sleep problems (Herculano-Houzel, n.d.). In addition, because network connectivity and modulatory control in these regions regulates the initiation of voluntary actions, dysfunction can result in disruptions to volitional control of behavior. Disruptions to this circuitry may also affect one's ability to inhibit prepotent responses and thereby increase impulsive behavior (Duff et al., 2010; Tupper, 2011).

1.5.2 EF in Huntington's Disease

EF systems are among the most vulnerable to decline in HD. HD is associated with reduced cortical thickness in EF-relevant brain regions including the frontal lobes (Dumas, 2013; Harrington et al., 2014). Pre-motor manifest HD is characterized by deficits in attention and working memory (Ciriegio et al., 2020; Harrington et al., 2014) and these domains continue to be impacted in addition to inhibitory control after the onset of motor symptoms (Ciriegio et al., 2022; Dumas, 2013). Beyond impacts on EF, processing speed is also affected across the disease course (Dumas, 2013; Harrington et al., 2014).

1.5.3 Depression symptoms in HD

The incidence of HD is quite low, with an estimated cumulative age-adjusted frequency rate of 6.52 per 100,000 persons in the United States (Bruzelius et al., 2019), and the vast majority of individuals with MDD do not have HD. However, the co-occurrence of HD with depression symptoms is quite high; the rate of depression among HD patients is double that of the general population (Paulsen et al., 2005). Cross-sectional data from a large cohort of patients with HD (*N* = 2,693) indicated that depression symptoms tend to peak immediately prior to diagnosis and decrease in later stages of the disease as apathy becomes more prevalent (Paulsen et al., 2005). The period immediately preceding diagnosis is typically associated with increased disability and reduced independence, which may increase risk for depression symptoms (Paulsen et al., 2005). Although functional impairment and pathology increase as the disease progresses and thus might be expected to be associated with increased depression symptoms over time, Paulson et al. (2005) speculate that the observed pattern of reduced depression symptoms over time may be related to adaption to illness, acceptance of the diagnosis, or reduced insight into current levels of disability. However, there is substantial variability in the onset and severity of depression symptoms over the disease course (Kim et al., 2015). A multivariate clustering analysis of the same cohort of patients showed that the level and slope of depression symptoms does not consistently correlate with progression of cognitive and motor symptoms, indicating that individuals with HD are susceptible to depression at any point in the disease course (Kim et al., 2015).

Limited existing data on the effects of depression on EF in individuals with prodromal HD indicates that depression is a significant predictor of performance on tasks assessing working memory and cognitive flexibility (Nehl et al., 2001; Smith et al., 2012). Depression is also associated with poorer processing speed among individuals with pre-motor manifest HD (Smith et al., 2012).

1.6 EF, Coping, and Emotion Regulation

The impact of psychiatric and medical conditions on EF may be far-reaching. Specifically, EF is critical for managing the high levels of stress faced by patients with a wide range of disorders and chronic health conditions. Patients with medical and psychiatric conditions face stressors related to their illness and the impacts of their changing physical and mental health on their families. Medical and psychiatric illnesses also commonly bring about significant financial burdens due to the costs of medical care and treatments and reduced income from missed work. These stressors may place patients at increased risk for psychological distress. The impact of stress on psychological functioning depends on the ability to flexibly adapt to (i.e., cope with) both static and dynamic stressors. Coping, defined as conscious purposeful efforts to regulate emotion, cognition, behavior, physiology, and the environment in response to stress (Compas et al., 2001), depends in part on intact and efficient EF (Compas, 2006). Relevant to RDoC, coping also includes the capacity to regulate emotions which is part of the arousal/regulatory dimension of RDoC.

One important correlate of EF is the set of strategies that individuals use to regulate emotions and cope with stress (Compas et al., 2009; Compas, Jaser, Bettis, et al., 2017; Morris et al., 2015; Snyder et al., 2015; Zelazo, 2020). To better understand how patients cope, it is important to consider how intact and efficient EF may support the ability to use specific cognitive coping strategies. In individuals with MDD, abnormal emotion processing may involve disruptions to both automatic and voluntary components of cognitive control (Phillips et al., 2008). In contrast to automatic responses to emotions, which are typically out of volitional control, coping is an aspect of voluntary cognitive control that includes processes such as deliberate distraction and cognitive reappraisal (Compas et al., 2001; Compas, Jaser, Bettis, et al., 2017).

1.6.1 Secondary control coping

In the control-based model of coping derived by confirmatory factor analysis, primary control coping describes efforts to directly change the source of stress while secondary control coping

describes efforts to *adapt* to the source of stress (Compas et al., 2001, 2020). Secondary control coping encompasses the strategies of cognitive reappraisal, positive thinking, acceptance, and distraction. Previous research suggests that secondary control coping strategies are particularly adaptive responses to unpredictable and uncontrollable stressors (e.g., Compas et al., 2012, 2014). Engaging with each of these strategies requires numerous EFs acting in concert: working memory capacity, cognitive flexibility, directing attention on purpose, sustaining attention, and inhibiting responses to distractors. For example, cognitive reappraisal requires an individual to be aware of a maladaptive thought (directing attention on purpose), consider alternatives (working memory; shifting), consider differences in their emotions as they consider alternate perspectives in turn (working memory; flexibility), and engage with a reappraised thought (sustained attention), all while inhibiting responses to internal and external stimuli that triggered the original thought (inhibition). Deliberate use of positive thinking, acceptance, and distraction to cope with stress engage the same core EFs to different degrees. The link between EF abilities and cognitive reappraisal in addition to other secondary control coping strategies has been established in several studies (e.g., Andreotti et al., 2013; Ciriegio et al., 2020, 2022; McRae et al., 2012; Moodie et al., 2020; Robinson et al., 2015).

1.6.2 Moderators of the association between EF and Coping

An individual's ability to use EFs to engage in cognitive coping strategies (namely, cognitive reappraisal, positive thinking, acceptance, deliberate distraction) may vary as a function of other aspects of cognitive function. The human brain demonstrates remarkable plasticity when isolated structures or functions are compromised. On imaging, this plasticity may manifest as increased activity in non-compromised brain regions to compensate for difficulties on a given task. For example, functional neuroimaging data from children completing a response inhibition task demonstrates that children with attention deficit/ hyperactivity disorder (ADHD) activate fewer frontal brain regions and more posterior and diffusive brain regions than children without ADHD,

while no significant differences in performance or accuracy were found between the two groups (Ma et al., 2012).

In adult populations, researchers investigating typical and atypical cognitive decline differentiate between "neural compensation" and "neural reserve." Neural compensation refers to the novel use of non-default brain regions after disease or healthy aging disrupts the default networks typically recruited to complete a given task (Martins et al., 2015). Neural reserve, on the other hand, refers to the availability of pre-existing neural resources for flexibly engaging with increasing task demands (Stern, 2009, 2017). As an example, an empirical study used functional neuroimaging to investigate distributions of neuronal activity of patients among patients with HD, and found evidence for reduced activation in cortical areas of EF networks, as well as reduced functional integration in both subcortical and cerebellar regions (Sarappa et al., 2017). Interestingly, activation in cerebellar regions was associated with performance-based EF measures, which the authors interpret as potential evidence for neural compensation (Sarappa et al., 2017). In terms of neural reserve, a recent review highlighted the role of basic attention functions and preserved knowledge in attenuating the effects of healthy aging on working memory (Naveh-Benjamin & Cowan, 2023). It is possible that some reserve factors and compensatory strategies may blunt the effects of aging and disease on functional outcomes.

Behaviorally, we might observe that an individual adapts their behavior or engages other cognitive strengths to compensate for new or increasing EF weaknesses. If inhibition is a key component of the common EF factor that supports updating and shifting (e.g., Friedman & Miyake, 2017; Miyake & Friedman, 2012), then individuals with declining inhibitory control may engage more updating or shifting capacities to compensate. Conversely, individuals affected by declining working memory or shifting may compensate by engaging more inhibitory control when completing tasks with high EF demands. Inhibitory control and working memory are interdependent. Inhibitory

control supports working memory by filtering out distractions to keep one's focus on the goal at hand. It serves a gating function such that useful information is gated in, and internal and external distractions are gated out from working memory capacity. Working memory also supports inhibitory control; knowing what to pay attention to and what to inhibit requires holding a goal in mind. The better someone is at keeping their goal (or a task instruction) in mind, the less likely they will be to make an error on their current task (Diamond, 2013).

1.6.3 The supporting role of processing speed

While there are many aspects of cognitive function that support EF, an important one is processing speed. The speed at which an individual processes information may affect the amount of information an individual can attend to and manipulate in working memory, thus contributing to a more efficient information-processing system (Hasher et al., 2008). In this way, processing speed may be viewed as a cognitive "resource" that can support or hinder EFs. Working memory and processing speed show parallel developmental trends, with both typically improving across early development and declining with age in later adulthood (Fry & Hale, 2000; Rozas et al., 2008; Zimprich & Kurtz, 2013). Indeed, there is evidence to support a developmental cascade in childhood whereby processing speed increases with chronological age and predicts improvements in working memory (Nettelbeck & Burns, 2010). Declining cognitive abilities in older adults are predicted by both working memory and processing speed (Nettelbeck & Burns, 2010), suggesting distinct causal pathways for the effect of both updating-specific capacities and speed of processing on overall cognition in typical aging. However, the direction of causality between EF and processing speed is unclear and may be better explained by a third variable (Diamond, 2002, 2013). Examining how variations in processing speed may affect the association between EF and functional outcomes of interest is important for improving our understanding of these pathways and their correlates.

Thus, while a portion of individual variation in engagement with secondary control coping is likely to be explained by the presence of psychopathology or neurodegenerative diseases and their impacts on EF systems, it is also possible that some of the variation will be explained by individuals' ability to use other EFs and supportive cognitive processes to carry out those same tasks.

1.7 Current study: Rationale and Hypotheses

The present study examined links between EF, processing speed, and coping in two samples of patients affected by either a neurodegenerative disorder (HD) or a mood disorder (MDD), two neuropsychiatric disorders described in the DSM-5-TR (American Psychiatric Association, 2022). It also compared models indicating that inhibitory control supports working memory (Friedman & Miyake, 2017; Miyake & Friedman, 2012) with those indicating working memory supports inhibitory control (Baddeley, 2012; Hasher et al., 2008) by testing the moderating effects for inhibitory control and working memory on the association between the other EF on secondary control coping in these two populations. Study aims and hypotheses are described below.

1.7.1 Aim 1. Examine absolute differences in EF performance compared to established norms.

1.7.1.1 *Hypothesis 1a.* Relative to established norms, individuals with MDD will perform significantly worse across all three measures of core EFs corresponding to working memory, inhibitory control, and shifting abilities.

1.7.1.2 *Hypothesis 1b.* Relative to established norms, individuals with HD will perform significantly worse across all three measures of core EFs corresponding to working memory, inhibitory control, and shifting abilities.

1.7.2 Aim 2. Examine between-group differences in performance on EF measures. Then, examine whether significant differences remain after accounting for depression symptom levels.

1.7.2.1 *Hypothesis 2a.* The HD group will perform significantly worse on across all three EF domains relative to the MDD group.

1.7.2.2 *Hypothesis 2b.* Current depression symptom level will not account for all the variance in EF performance between groups. That is, a significant portion of the variance will remain accounted for by disease group after accounting for depression symptom level.

1.7.3 Aim 3. As an exploratory aim, examine characteristic patterns of EF performance within and between groups.

1.7.3.1 Hypothesis 3a. There will be a main effect of group such that individuals with HD will perform worse than individuals with MDD across all three measures of EF.

1.7.3.2 *Hypothesis 3b.* There will be a main effect of domain such that there will be larger deficits in inhibitory control and working memory relative to shifting.

1.7.3.3 *Hypothesis 3c.* There will be a significant group by domain interaction such that individuals with HD will exhibit more impairment on inhibitory control relative to other areas of EF, and individuals with MDD will exhibit more impairment on working memory relative to other areas of EF.

1.7.4 Aim 4. As a second exploratory aim, explore interactions between multiple elements of EF and processing speed on coping.

1.7.4.1 *Hypothesis 4a.* In the MDD sample, inhibitory control will moderate the association of working memory with secondary control coping such that better inhibitory control attenuates the effect of working memory on secondary control coping (Figure 1a).

1.7.4.2 *Hypothesis 4b.* In the HD sample, working memory will moderate the association of inhibitory control with secondary control coping such that better working memory attenuates the effect of inhibitory control on secondary control coping engagement (Figure 1b).

1.7.4.3 *Hypothesis 4c.* In both samples, processing speed will also moderate the association of X

(either inhibitory control (HD) or working memory (MDD)) with secondary control coping such that, at higher levels of processing speed ability, the effects of X on coping will be attenuated (Figures 1c-1d).

2 METHOD

2.1 Samples

Data from two samples were included in the present study: individuals affected by HD and individuals with a history of MDD. All participants completed a baseline neurocognitive assessment as part of broader studies. Both studies enrolled both parents and offspring, but only data from affected parents were used in the present study.

2.1.1 MDD Sample

The first sample includes parents with a history of MDD who participated in a study testing the efficacy of a family depression preventive intervention (NIMH grants R01MH00260 and R01MH100258; Compas, Garber, & Weersing, PIs). Recruitment efforts included advertisements in mental health care settings and general medical settings, as well as outreach via local media. Parent–child dyads were eligible for the study if the parent had experienced a major depressive episode during their child's lifetime, as assessed by phone screen and diagnostic interview. Study procedures were reviewed and approved by Institutional Review Boards at Vanderbilt University and San Diego State University. Informed consent and assent were obtained from all parents and offspring prior to study enrollment and participation.

Around the midpoint of baseline data collection, the platform on which the NIH Toolbox Cognition Battery (NIHTB-CB; described in Section 2.2) was administered changed from the desktop version to the iPad version. One hundred five parents provided complete data on the NIHTB-CB on the iPad. Only this subset of parents was included in analyses to facilitate more accurate comparisons with the HD sample, all of whom completed these measures on the iPad-administered version of the NIHTB-CB. Of this subset (n =105), 89.3% identified as female. 85% (n =87) of participants reported their age: M age = 42.77 ± 6.33 years; range= 29-58. 90% (n =95) self-reported their race: 70.5% White; 9.5% Black/African American; 4.2 % Asian; 2.1% Native

Hawaiian or Other Pacific Islander; 10.5% Multiracial; 3.2% reported "Other". 93% (*n* =98) reported their ethnicity: 15.3% Hispanic or Latinx.

2.1.2 HD Sample

This sample is comprised of adult patients with HD. Families were invited to participate in an ongoing series of studies enrolling families affected by HD including study R01 HD104188-01 (Compas & Claassen, PIs). Recruitment occurred via patient review of patients receiving care through the Vanderbilt University Medical Center Huntington Disease Society of America Level 1 Center of Excellence (COE) from October 2018 through February 2022. Eligibility requirements included (a) participants must use English as their primary language, (b) patients with HD must be part of the Huntington's Disease COE, and (c) patients with HD may range in disease severity (i.e., presymptomatic, prodromal, manifest). When both a parent and their HD-affected offspring were present in the sample and provided complete data on neurocognitive measures, the patient whose age most closely matched the mean of the MDD sample (*M* age = 42.77 years) was retained for analyses. This decision was made to reduce within-family effects and increase comparability between samples.

The dataset used in the present study included 82 patients who completed performance-based EF measures. Patients were 58.5% female; *M* age = 42.17 ± 12.43 years; range = 17-72 years. Patients self-reported race (97.6% White; 1.2% Black/African American; 1.2% Native Hawaiian/Pacific Islander) and ethnicity (3.8% Hispanic or Latino). Although HD can affect individuals of all ethnic and racial backgrounds, it most commonly affects individuals of European descent (Bates et al., 2015), as reflected in our sample demographics.

Informed consent was obtained from all participants prior to study enrollment and participation. This study was reviewed and approved by the Vanderbilt University Institutional Review Board. The

medical director of the COE (Daniel Claassen, MD) oversaw the recruitment of eligible families, and a member of the clinical team at the COE made the initial study introduction.

2.2 Measures

2.2.1 Demographics

Participants provided demographic information, including age, sex, race, and ethnicity, as part of the initial data collected prior to administration of the neurocognitive battery.

2.2.2 Executive Functioning

Three subtests from the NIH Toolbox Cognition Battery (NIHTB-CB) were used to assess domains of EF, and a fourth subtest was used to examine the role of processing speed in supporting EF. The National Institutes of Health initiated the development of the NIHTB-CB (Weintraub et al., 2013; Zelazo et al., 2013) to measure neurocognitive outcomes across the lifespan. The measure has been normed on samples ages 3-85 years. Measured domains include attention, processing speed, various aspects of memory, and the ability to plan and execute tasks in a goal-directed manner. Originally developed for administration on a desktop computer, it can now be administered on an iPad. Following administration, raw scores are automatically converted to age-corrected standard scores. Each subtest included in this study is described in more detail below.

Flanker Inhibitory Control and Attention (FICA) measures attention and the ability to inhibit automatic responses. Participants are asked to focus on the central stimulus and inhibit attention to the flanking stimuli. Congruent (all stimuli pointing the same direction) and incongruent (center stimulus pointing a different direction than the flanking stimuli) trials are presented in a mixed manner.

Dimensional Change Card Sort Test (DCCS) assesses executive function and set shifting/cognitive flexibility. Two target pictures are presented that vary in shape and color. Participants match a shape or color stimulus to a target visual stimulus. The relevant dimension for

sorting is indicated by a cue word (i.e., "shape" or "color").

List Sorting Working Memory (LSWM) assesses both immediate recall and sequencing of stimuli. Participants are asked to remember and sort objects in order of size. In the one-list condition, participants sort a series of objects from a single category (food or animals). In the two-list condition, participants are presented with objects from two categories, and sort objects from one category before sorting objects from the second category.

Pattern Comparison Processing Speed Test (PCPS) measures processing speed using visually presented stimuli. Participants are presented with two side-by-side pictures and asked to discern whether the pictures are the same or not. They select their response from YES or NO buttons on the iPad screen.

In contrast to many neuropsychological batteries, which include measures that have been normed on different samples, the domains of the NIHTB-CB were developed simultaneously and normed together such that the data can be used to compare performance across samples and studies (Tulsky et al., 2014; Weintraub et al., 2013; Zelazo et al., 2013). However, there is some evidence to suggest a need for renorming that may affect the present data. In one study, participants (N =62 combat veterans) were randomly assigned to complete the NIHTB-CB on the desktop first or the iPad fist, then also completed it on the other platform (Brearly et al., 2019). Scores were compared to assess for need for renorming based on the change in platform. Results indicated a 10-point difference in standard scores when comparing performance on the FICA test when administered on the desktop (M =100) versus the iPad (M =90), whereas score differences between platforms ranged from 3-6 points for other tests in the NIHTB-CB (Brearly et al., 2019). I elected to include only scores from tests administered on the iPad to enhance comparability between groups, but results from (Brearly et al., 2019) suggest that scores on the FICA may need to be adjusted to be accurately

compared with other tests within groups. Results will be interpreted with and without these possible adjustments.

2.2.3 Coping

The Responses to Stress Questionnaire (Connor-Smith et al., 2000) is a self-report measure used to assess both sources of stress and coping strategies in response to stressful experiences. The measure has been adapted to ask specifically about stressful experiences related to parenting with depression (RSQ-PD; Jaser et al., 2005), and to stress related to HD (RSQ-HD; Ciriegio et al., 2022). It is structured in two parts. In the first part of the questionnaire, participants are provided with a list of 10 representative stressors specific to their circumstances. In the RSQ-PD, these stressors include feeling like they are not meeting their child's needs, not wanting to do things with the family, or feeling as if they are burdening others with their emotions (Connor-Smith et al., 2000; Jaser et al., 2005). In the RSQ-HD, sources of stress include concerns about the future, loss of independence/ability to care for self and dependents, and feeling isolated or different from peers (Ciriegio et al., 2022). Participants are asked to indicate how stressful the listed experiences have been for them in the preceding six months. These items serve to prime the respondent to think about sources of stress related to the condition of interest when completing the subsequent coping section.

For both versions of the RSQ, this second section is comprised of 57 items reflecting coping and automatic responses to stressors. Participants are asked to rate how often they use each strategy or have a response; each item is rated on a 4-point scale (from "Not at all" to "A lot"). To compute relative engagement with five factors of coping and response to stress (i.e., primary control engagement coping, secondary control engagement coping, disengagement coping, involuntary engagement, and involuntary disengagement), proportion scores are computed as the use of a particular type of coping relative to the total score obtained on the RSQ. The current study focuses

on the secondary control engagement coping factor, as previous work has shown that the coping strategies subsumed by the secondary control factor (acceptance, cognitive reappraisal, distraction) are most adaptive in dealing with uncontrollable stressors (Aldao et al., 2010; Compas et al., 2012, 2014; Compas, Jaser, Bettis, et al., 2017), such as inheriting the genetic mutation for a neurodegenerative disorder or coping with a chronic disease. The RSQ has demonstrated excellent internal consistency, test–retest reliability, and convergent and construct validity (Connor-Smith et al., 2000).

2.2.4 Symptoms of depression

The majority of participants (n = 51 from the HD sample; n = 98 from the MDD sample) completed the Patient Health Questionnaire-9 (PHQ-9; Kroenke et al., 2001) to report on depression symptoms in the preceding two weeks. This measure is based on DSM-5 symptom criteria for MDD, and is well-validated, widely used, and demonstrates good reliability. Other participants from the HD sample (n = 23) completed the Achenbach System of Emotional and Behavioral Assessment (ASEBA; Achenbach & Rescorla, 2001, 2003) Adult Self-Report (ASR) (Achenbach et al., 2002) to report on depression symptoms over the preceding six months. The normative sample for the ASR is representative of the US population, and the measure has been shown to have excellent internal consistency, test-retest reliability, and construct validity (Achenbach et al., 2002). It yields both empirically derived subscales related to internalizing symptoms and subscales that are derived from DSM-5 symptom criteria for MDD (i.e., "Affective Problems"). For participants who completed with ASR, *T*-scores from the "Affective Problems" subscale were used to align most closely with symptom reports on the PHQ-9.

2.3 Data analysis

2.3.1 Data reduction and transformations

Subtests from the NIHTB-CB are automatically scored; raw scores are converted to standardized scores (M = 100; SD = 15) that are normed with respect to participant age. Scores on the "Affective Problems" ASEBA scale and raw scores from the PHQ-9 were converted to z-scores to enhance comparability of symptom levels between samples and measures. Specifically, z-scores were computed for raw scores on the PHQ-9, such that the reference point reflects the mean for that sample on that measure. Similarly, z-scores on the "Affective Problems" subscale on the ASEBA were computed for participants who reported on their depressive symptoms using this measure. Thus, a z-score of 0 indicates that an individual's symptom level fell at the mean symptom level for their sample (i.e., HD or MDD) on that measure. Distributions of all continuous variables were inspected for normality. Outlier correction (i.e., Winsorizing) and data transformations was performed as indicated by visual inspection and skew statistics.

2.3.2 Analytic Plan

All statistical analyses were performed in R (R Core Team, 2023). Multivariate analysis of variance (MANOVA) and mixed analysis of variance (mixed ANOVA) models were conducted using the 'rstatix' package (Kassambra, 2023), while multivariate analysis of covariance (MANCOVA) analyses were conducted using tools from the 'jmv' package (Selker et al., 2022).

2.3.2.1 *Aim 1. Examine absolute differences in EF performance compared to established norms.* I addressed this aim using multivariate *t*-tests within both samples. First, I conducted a one-sample Hotelling's T^2 test to test if MDD sample means on LSWM, FICA, DCCS were different from NIHTB-CB norms. Second, I conducted a parallel one-sample Hotelling's T^2 test to test if HD sample means on LSWM, FICA, DCCS were different from NIHTB-CB norms. When the omnibus tests were significant, I followed up these tests with one-sample *t*-tests, comparing observed means to 100 (i.e., the mean of the normative data).

2.3.2.2 Aim 2. Examine between-group differences in performance on EF measures. Then, examine whether significant differences remain after accounting for depression symptom levels. To address this aim, I first conducted a multivariate analysis of variance (MANOVA) to evaluate the effect of disease group (categorical independent variable) on EF performance (multiple continuous dependent variables). Next, I conducted a multivariate analysis of covariance (MANCOVA) to evaluate the effect of disease group on EF performance, while including depression symptom level as a covariate. Significant omnibus tests were followed by appropriate post-hoc tests, selected based on results of preliminary tests evaluating whether assumptions were met (see Appendix).

2.3.2.3 *Aim 3. Examine characteristic patterns of EF performance within and between groups.* To address this aim, I conducted a 2 x 3 mixed ANOVA to examine the main effects of group and domain as well as the interaction between group and domain on EF performance across the three domains. Significant effects were probed using one-way ANOVA and followed by pairwise comparisons to determine which associations were driving overall effects.

2.3.2.4 *Aim 4. Explore interactions between multiple elements of EF and processing speed on coping.* EF abilities in one area may compensate for deficits in other areas and support engagement in secondary control coping. To explore this aim, I ran a series of moderation models with a secondary EF and processing speed entered as moderators of the association between X (primary EF) and Y (secondary control coping). For the MDD sample, I examined whether better performance on a measure of common EF (i.e., inhibitory control) attenuated the effects of working memory on secondary control coping (Figure 1a). In the HD sample, I examined whether better working memory attenuated the effects of inhibitory control on secondary control coping (Figure 1b). Finally, I examined the role of processing speed, a cognitive capacity that supports EF, in moderating the effect of EF on coping (Figures 1c-

d). The introduction of an interaction predictor can increase the risk of multicollinearity and result in coefficient estimates with erroneously high standard errors. Variables were mean-centered to reduce the problem of multicollinearity and to aid in the interpretability of regression coefficients (e.g., Schielzeth, 2010).

2.3.3 Statistical power

Power analyses were run in G*Power version 3.1 (Faul et al., 2007) to determine the sensitivity of the multivariate *t*-tests, univariate *t*-tests, MANOVA, MANCOVA, mixed model ANOVA, and regression analyses described above. The following parameters were included for each sensitivity analysis: two-tailed tests; probability of a type I error (α) = 0.05; power ($1-\beta$) = 0.80. Initially, sample size for the HD sample was set to n = 82, and sample size for the parental MDD sample was set to n = 105.

Sensitivity: Multivariate and univariate t-tests. A sensitivity analysis for a one-sample Hotelling's T^2 test to test the difference between patient performance on EF measures (i.e., three dependent variables) relative to normed samples indicates that this analysis was powered to detect a minimum effect size of d = 0.37 in the HD sample and d = .33 in the MDD sample. For the post-hoc one-sample univariate *t*-tests, this analysis was powered to detect a minimum effect size of d = 0.31 in the HD sample and d = .28 in the MDD sample. Cohen's effect size guidelines (Cohen, 1992) for interpreting d are used such that .20, .50, and .80 indicate small, medium, and large effects, respectively. Taken together, this set of comparisons was powered to detect effects that are small to medium in magnitude.

Sensitivity: ANOVA models. The sensitivity analysis for ANOVA models included the following additional parameters: number of groups (k) = 2; numerator degrees of freedom = 3; total sample size = 187. In these analyses, the computed effect size f represents the proportion of variance accounted for in the sample relative to the proportion of variance left unaccounted for.

Cohen's effect size guidelines (Cohen, 1992) for interpreting *f* are used such that .10, .25, and .40 indicate small, medium, and large effects, respectively. Sensitivity analyses for the ANCOVA test with one covariate indicated that the test was powered to detect an effect size $f = 0.24$, indicating that the analysis is sufficiently powered to detect effects that are small to medium in magnitude.

Sensitivity analyses for the MANOVA models indicated that the omnibus test was powered to detect global effects at the level of $f^2(V) = 0.060$. To determine sensitivity for the between-group, within-group, and within*between interaction effects, the correlation among dependent variables was set to .61, equal to the average of the actual correlation among the dependent variables included in the analyses. Sensitivity analyses indicated that MANOVA models were powered to detect between-factor effect sizes of $f^2(V) = 0.177$, within-factor effect sizes of $f^2(V)$: 0.083, and within*between interaction effect sizes of $f^2(V)$: 0.229. In these analyses, the computed effect size f^2 represents local effect size, or one variable's effect size in the context of a multivariate regression model (Selya et al., 2012). Cohen's effect size guidelines for interpreting f^2 (Cohen, 1992) were used such that .02, .15, and .35 indicate small, medium, and large effects, respectively. Thus, these ANOVA models were sufficiently powered to detect effects that are small to medium in magnitude or larger.

Sensitivity: Moderation analyses. The number of predictors included in the sensitivity analysis for the planned linear multiple regression analyses was set to three, corresponding to the inclusion of two EF domains (or processing speed) and one interaction term in each model.

For the HD sample ($n = 82$), analyses indicated the multiple linear regression model was powered to detect an effect size $f^2 = 0.14$ when three predictors were included. For the MDD sample ($n = 105$), analyses indicated the multiple linear regression model was powered to detect an effect size $f^2 = 0.11$. Taken together, the regressions were sufficiently powered to detect effects that are small to medium in magnitude or larger.

3 RESULTS

3.1 Preliminary analyses

3.1.1 Missing data

Missing data for each of the variables included in the analysis ranged from 0-10%. For the cognitive variables, 0.5% of DCCS scores, 1.1% of FICA scores, 2.7% of LSWM scores, and 1.1% of PCPS scores were missing from the full dataset. The proportion of data that were missing was higher on the depression symptom Z-score (8.0%) and the measure of secondary control coping (9.6%) because survey data was often collected separately from the study visit where the NIHTB-CB was completed.

As a first step to addressing missing data, Little's test statistic (Little, 1988) was used to assess if data were missing completely at random (MCAR). The MCAR assumption was tested separately for the HD sample data and for the MDD sample data, and there was no evidence that the data were not missing completely at random in either dataset. Additionally, in the HD sample, demographic variables (age, sex, race) were not associated with a binary variable indicating missingness (i.e., 1= missing data; 0 = no missing data on any variable). A parallel analysis was not run in the MDD sample because there was some missing data on demographic variables in this dataset. Therefore, an auxiliary variable approach was not used.

Next, multiple imputation was performed using the 'mice' package in R (Buuren & Groothuis-Oudshoorn, 2011) to address missing values in cognitive test scores, the depression symptom Z-score, and the proportion score for secondary control coping. This package imputes variables based on fully conditional specification and chained equations, whereby each imputed variable is imputed by a separate model. Generated multivariate imputations were used to complete the dataset for subsequent analyses.

3.1.2 Bivariate correlations

Summary statistics and bivariate correlations among each of the variables used in subsequent analyses are presented for each group in Table 1. Cohen's (1988) conventions were used to interpret effect sizes, such that *r*'s = .10, .30, and .50 corresponded to small, medium, and large effects, respectively. As expected, there were large positive associations among EF domains in the HD sample (*r*'s = .56-.69). In the MDD sample, there was a large association between shifting and inhibitory control domains ($r = .59$), a medium association between shifting and working memory ($r = .42$), and a small association between working memory and inhibitory control ($r = .18$).

In the HD sample, there were small positive associations between use of secondary control coping and all three EF domains: shifting $r = .21$; inhibitory control $r = .22$; working memory $r = .23$. These were small positive correlations between shifting ($r = .14$) and working memory ($r = .21$) and use of secondary control coping in the MDD sample. There was not a significant association between the inhibitory control domain and secondary control coping in the MDD sample, nor were there significant correlations between EF domains and depression symptom levels in either sample. Medium to large negative correlations between secondary control coping engagement and depression symptom levels were present in both samples ($r = -.58$ in the HD sample; $r = -.44$ in the MDD sample); more engagement in secondary control coping was strongly associated with lower depression symptom levels.

Preliminary tests addressing the assumptions required for analysis of variance family of tests are summarized in the Appendix. When assumptions were violated, the decision or action step taken to proceed with the analysis is reported. Specifically, because there was evidence that the assumption of homogeneity of variances was violated for some variables as well as unequal sample sizes (see Appendix), Welch's *t*-tests and Games-Howell tests were used for post hoc tests and Pillai's trace was selected as the test statistic for multivariate analyses.

3.2 **Aim 1.** *Examine absolute differences in EF performance compared to established norms.*

A one sample Hotelling's T^2 test was used to test if a set of vectors comprised of scores on three NIHTB-CB tests had means equal to a hypothetical mean (μ=100), with the alternative hypothesis being that the true value does not equal 100. For the HD sample, a one-sample multivariate Hotelling's T^2 test indicated significant differences between sample performance and established norms on at least one of the three tests: T^2 (3, 79) = 112.61, $p < .001$. For the MDD sample, a one-sample multivariate Hotelling's T^2 test also indicated significant differences between sample performance and established norms on at least one of the three tests: T^2 (3, 102) = 74.20, $p < .001$. Both omnibus tests were significant, therefore post-hoc one-sample *t*-tests comparing observed means on each of the subtests to 100 for each sample were conducted.

In the HD sample, a one-sample *t*-test comparing DCCS scores (*M* = 86.09, 95% CI [81.87, 90.30]) to the normative mean (μ = 100) indicated that the sample performed significantly worse than established norms in the shifting domain: $t(81) = -6.57$, $p < .001$. A one-sample *t*-test comparing FICA scores (*M* = 74.54, 95% CI [71.56, 77.52]) to the normative mean (μ = 100) indicated that the sample performed significantly worse than established norms on inhibitory control: $t(81) = -17.00$, $p < .001$. A one-sample *t*-test comparing LSWM scores (*M* = 85.44, 95% CI [81.49, 89.39]) to the normative mean (μ = 100) indicated that the sample also performed significantly worse than established norms on working memory: $t(81) = -7.33$, $p < .001$.

In the MDD sample, DCCS scores (*M* = 107.95, 95% CI [104.50, 111.41]) were significantly *above* the normative mean (μ= 100), indicating that the sample performed significantly better than established norms in the shifting domain: $t(104) = 4.57$, $p < .001$. FICA scores (*M* = 89.74, 95% CI [87.42, 92.06]) were significantly worse than established norms: $t(104) = -8.77$, $p < .001$. LSWM

scores (M = 100.95, 95% CI [98.16, 103.74]) were not significantly different from established norms: $t(104) = 0.68$, $p = .50$. Results of these multivariate and univariate t-tests are summarized in Table 2.

3.3 Aim 2. *Examine between-group differences in performance on EF measures. Then, examine whether significant differences remain after accounting for depression symptom levels.*

Results from a multivariate analysis of variance (MANOVA) indicated that there was a statistically significant difference between the groups on the combined dependent variables (DCCS, FICA, LSWM): $F(3, 1183) = 29.10$, $p < .001$, $V = .32$ (see Figure 2 and Table 3a). Post-hoc Welch tests revealed that there was a statistically significant difference in performance across shifting ($F(1, 167) = 64.80$, $p < 0.001$), inhibitory control ($F(1, 163) = 66.68$, $p < .001$), and working memory ($F(1, 153) = 40.98$, $p < .001$) domains between the groups. Games-Howell pairwise comparisons were used because the data violated the assumption of homogeneity of variances (see Appendix for results of preliminary analyses). All pairwise comparisons were significant for each of the outcome variables (DCCS, FICA, LSWM), with the MDD sample outperforming the HD sample on all three domains. The results of these post-hoc tests are summarized in Table 3b.

Results from a MANCOVA indicated that, after adjustment for concurrent depression symptom level, there remained a statistically significant difference in EF test scores between the groups, $F(3, 182) = 29.21$, $p < .001$, $V = .32$. There was no significant effect of depression symptoms of EF test scores $F(3, 182)=0.66$, $p = .58$, $V = .01$. In univariate analyses, there were statistically significant differences between groups on all three EF domains: shifting: $F(1,184) = 66.40$, $p < .001$; inhibitory control: $F(1,184) = 68.73$, $p < .001$; working memory: $F(1,184) = 43.09$, $p < .001$. There were no significant effects of depression symptoms as a covariate on dependent variables. Results of these tests are summarized in Table 4a.

Despite a non-significant effect of the covariate, post hoc analyses of covariance (ANCOVA) were conducted to examine the magnitude of group differences in EF scores using estimated marginal means. Results from ANCOVA tests are summarized in Table 4b. Post hoc pairwise comparisons indicated that the MDD sample significantly outperformed the HD sample on all three domains even after accounting for depression symptom level (Table 4c). Bonferroni correction for multiple comparisons was used. For the shifting domain, the difference in means between the MDD group and the HD group was 22.11, Cohen's d= 1.20, $t(184) = 8.13$, SE = 2.72, (Bonferroni adj) $p < .001$; see Figure 3a. For the inhibitory control domain, the difference in means between the MDD group and the HD group was 15.44, Cohen's $d = 1.22$, $t(184) = 8.27$, SE = 1.87, (Bonferroni adj) $p < .001$; see Figure 3b. In the working memory domain, the difference in means between the MDD group and the HD group was 15.53, Cohen's $d = 0.97$, $t(184) = 6.55$, SE = 2.37, (Bonferroni adj) $p < .001$; see figure 3c.

3.4 Aim 3. *Examine characteristic patterns of EF performance within and between groups.*

As a first step to examining within-group effects, average scores by group were visually inspected with a box plot (Figure 4). Visual inspection suggested that there may be substantial within-group differences, particularly when comparing performance in the inhibitory control domain to performance in the shifting and working memory domains.

An ANOVA test using type III sums of squares is recommended when sample sizes between groups are unequal, so a type III 2 x 3 mixed model ANOVA was conducted. Results indicated significant main effects of group ($F(1, 185) = 86.05$, $p < .001$, $\eta 2 = .24$), domain ($F(1.89, 348) = 86.24$, $p < .001$, $\eta 2 = .14$), and a group by domain interaction ($F(1.89, 348) = 5.30$, $p < .01$, $\eta 2 = .01$). Results from this omnibus test indicated that differences between groups differ in magnitude as a function of EF domain. Main and interaction effects are summarized in Table 5a.

If an interaction is present in a type III test, the main effects associated with that interaction are still somewhat interpretable because they are computed taking the interaction into account. However, main effects should be interpreted with caution, given that a significant interaction obscures the meaning of simple effects. Thus, simple effects are reported here, but are intended to be interpreted within the context of a significant interaction. Welch ANOVA tests and Games-Howell post hoc comparisons were performed, given evidence that homogeneity was violated (see Appendix).

Considering the Bonferroni adjusted *p*-value, the simple effect of group was significant for each EF domain: shifting: $F(1, 167) = 64.80$, (Bonferroni adj) $p < .001$; inhibitory control: $F(1, 163) = 66.68$, (Bonferroni adj) $p < .001$; working memory: $F(1, 153) = 40.98$, (Bonferroni-adj) $p < .001$. Pairwise comparisons indicated that performance on all three domains was significantly different between the two groups (all Bonferroni adjusted *p*'s < .001), with the MDD sample outperforming the HD sample in each domain (see Table 5b).

Considering the Bonferroni adjusted p-value, the simple effect of EF domain was significant for the MDD group: $F(2, 202) = 42.80$, (Bonferroni adj) $p < .001$, and for the HD group: $F(2, 157) = 14.74$, (Bonferroni adj) $p < .001$ (see Table 5c). Collapsing across samples, pairwise comparisons between domains yielded significant differences in performance between the shifting and inhibitory control domains $t(329) = 8.01$, (Bonferroni adj) $p < .001$ and between the inhibitory control and working memory domains $t(360) = 6.61$, (Bonferroni adj) $p < .001$, but not between the shifting and working memory domains $t(359) = 2.01$, (Bonferroni adj) $p =$ ns (see Table 5c). Results suggest that relatively lower scores in the inhibitory control domain drove this effect.

To probe the significant interaction effect, pairwise comparisons between domains were conducted at each group level, using paired *t*-tests because data represent repeated measures within subjects. Within the MDD group, there were significant differences in performance between: the

shifting and inhibitory control domains: $t(181) = 8.68$, (Bonferroni adj) $p < .001$; the shifting and working memory domains: $t(199) = 3.13$, (Bonferroni adj) $p < .01$; and the inhibitory control and working memory domains: $t(201) = 6.13$, (Bonferroni adj) $p < .001$. On average, individuals in the MDD sample performed better on the shifting domain than on the inhibitory control and working memory domains, and better on the working memory domain than on the inhibitory control domain.

Within the HD group, there were significant differences in performance between: the shifting and inhibitory control domains: $t(144) = 4.43$, (Bonferroni adj) $p < .001$ and between the inhibitory control and working memory domains: $t(150) = 4.49$, (Bonferroni adj) $p < .001$, but not between the shifting and working memory domains: $t(161) = 0.13$, p = ns. On average, individuals in the HD sample performed better on shifting and working memory than on the inhibitory control domain, but their performance on the shifting relative to the working memory domain did not differ significantly. These results are summarized in Table 5d.

3.5 **Aim 4.** *Explore interactions between multiple elements of EF and processing speed with coping.*

Four linear models with two predictors and an interaction term were run to examine the associations of multiple aspects of cognitive function with secondary control coping. The first two models examined whether an additional EF would have an additive or multiplicative effect on the link between a primary EF and secondary control coping. Specifically, the first model examined whether, in the MDD sample, the association between working memory and use of secondary control coping was moderated by inhibitory control. Results indicated that neither the main effects of working memory or inhibitory control nor the interaction between working memory and inhibitory control were significant (p's > .05; Table 6a); overall $F(3,101) = 0.88$, $p = .45$, adjusted $R^2 = 0.00$). The second model examined whether, in the HD sample, the association between inhibitory

control and use of secondary control coping was moderated by working memory. Results indicated that neither the main effects of inhibitory control or working memory nor the interaction between inhibitory control and working memory were significant (*p*'s > .05; Table 6b); overall $F(3,78) = 2.33$, $p = .08$, adjusted $R^2 = 0.05$.

The next two models examined processing speed as a potential moderator of the association between EF and secondary control coping. Specifically, the third model examined whether, in the MDD sample, the association between working memory and use of secondary control coping was moderated by processing speed. Neither the main effects of working memory or processing speed nor the interaction between working memory and processing speed were significant (*p*'s > .05; Table 6c); overall $F(3,101) = 0.73$, $p = .53$, adjusted $R^2 = -0.01$. The fourth model examined whether, in the HD sample, the association between inhibitory control and use of secondary control coping was moderated by processing speed. Neither the main effects of inhibitory control or processing speed nor the interaction between inhibitory control and processing speed were significant (*p*'s > .05; Table 6d); overall $F(3,78) = 1.80$, $p = .15$, adjusted $R^2 = 0.03$.

4 DISCUSSION

4.1 Summary of Findings

The present study examined absolute and relative differences in performance on EF measures from the NIHTB-CB (measuring shifting, inhibitory control, and working memory) in a sample of adults with a history of depression (MDD sample) and in a sample of adults with HD (HD sample). Exploratory analyses investigated whether EFs predicted use of secondary control coping, and whether that association was moderated by other EFs or by processing speed.

In preliminary bivariate correlation analyses, positive correlations ranging from small to large in magnitude emerged among all EF variables in both samples. Shifting, inhibitory control, and working memory demonstrated small positive correlations with secondary control coping in the HD sample. In the MDD sample, shifting and working memory demonstrated small positive correlations with secondary control coping but there was not a significant correlation between inhibitory control and secondary control coping. There were, however, medium to large negative associations between secondary control coping and depression symptom levels in both samples.

Results from a multivariate test addressing the first aim (i.e., to examine absolute differences in EF performance compared to established norms) indicated that score means from both samples differed from norms in at least one domain. Subsequent univariate tests revealed that the HD sample performed significantly below established norms in all three EF domains (shifting, inhibitory control, and working memory). A more variable pattern emerged from univariate tests comparing the MDD sample to established norms. While this sample performed significantly below established norms in the inhibitory control domain, their scores did not differ from established norms in the working memory domain, and they performed significantly *better* than established norms in the shifting domain.

Relative to established norms, the most marked deficits in both groups were observed on the test assessing inhibitory control (FICA). These differences in FICA scores are substantial and may be related to need for renorming on this test. Specifically, as noted above, Brearly et al. (2019) found that standardized scores on the FICA test were 10 points lower when the same participants were randomly assigned to complete the test on the iPad relative to the desktop version, suggesting that the change in platform significantly impacted performance and contributed to an iPad-score disadvantage. Hypothetically, if scores on the FICA were approximately 10 points higher for each of the samples in the present study, then the magnitude of the difference between FICA scores in the MDD group would not have differed significantly from the norms (i.e., adjusted M =100). FICA scores in the HD group would still have been approximately one standard deviation below the normative mean (i.e., adjusted M = 84), but would no longer differ substantially from other within-group EF scores (observed Ms = 85-86). Given the findings from (Brearly et al., 2019), and in light of the approximately 10-point differences between FICA scores and other EF scores within the samples in the present study, it is important to consider that observed differences may be, in part, explained by an unaddressed need for renorming of the FICA when administered on the iPad.

With or without an adjustment, individuals with HD performed worse than established norms on all three measure of core EFs, consistent with Hypothesis 1(a) and previous literature (Ciriegio et al., 2020, 2022; Dumas, 2013; Harrington et al., 2014). Contrary to Hypothesis 1(b), individuals in this sample of patients with a history of MDD did not perform worse than established norms in the shifting or working memory domains. They did perform worse than established norms in the inhibitory control domain, but this effect would not be maintained after a possible 10-point adjustment due to the effects of administering this subtest on the iPad. While this pattern of findings is inconsistent with previous meta-analyses (Ahern & Semkovska, 2017; Nikolin et al., 2021; Rock et al., 2014; Snyder, 2013), including meta-analytic findings on EF in samples remitted from MDD

(Semkovska et al., 2019), it is possible that the observed pattern is related to the characteristics of the specific sample recruited for the broader study. Because it was an intervention trial to prevent the transmission of depression from parents to at-risk offspring, parents who enrolled in the study may have been higher functioning than other samples of adults with remitted depression. By enrolling in the study, they were signifying that they were motivated to participate in an intervention program to improve their parenting and help their children. The study activities (i.e., attending weekly group sessions, learning and practicing parenting skills) may have attracted a sample that was, in a sense, more cognitively recovered and resilient to EF deficits, at least enough to believe they would be able to coordinate the logistics and manage the work involved in completing the program. It is possible that they may have exhibited deficits in EF during a previous episode of depression, but that those deficits remitted along with their other symptoms.

The second aim involved examining relative, between-group differences in performance on EF measures and then examining whether significant differences remained after accounting for depression symptom levels. Consistent with Hypothesis 2a, results indicated that the two groups differed in their performance in all three domains and, in each domain, the MDD sample performed better than the HD sample. After accounting for depression symptom level, there remained a statistically significant difference in EF test scores between the groups, and there was no significant effect of the depression symptom level covariate on EF test scores, consistent with Hypothesis 2b. In fact, the group differences in estimated marginal means on each subtest were large in magnitude (Cohen's *d* ranged from 0.97-1.22). Findings from this set of analyses indicate that current depression symptoms were not accounting for a significant portion of the variance between the two groups. This suggests that group-level differences are not wholly attributable to depression symptoms and that other disease-related factors likely explain additional variance.

The third aim sought to elucidate characteristic patterns of EF performance by examining both within- and between-group differences in performance in each EF domain. Findings from analyses addressing this aim indicated that there was a main effect of group on performance for each of the three EF domains, with the MDD sample outperforming the HD sample in all three domains, consistent with Hypothesis 3(a). There was also a main effect of EF domain on the differences between groups; when scores were collapsed across groups, relatively low scores in the inhibitory control domain drove this overall effect. Finally, there was a significant group by domain interaction, suggesting that differences between groups differed across domains. Post hoc score comparisons indicated that, within the MDD sample, participants on average performed better on shifting than on working memory or inhibitory control, and that they performed significantly better on working memory than on inhibitory control. Within the HD sample, participants on average performed better on shifting than on inhibitory control, better on working memory than on inhibitory control, and approximately the same on shifting and working memory.

Results provided partial support for Hypothesis 3(b), which predicted a main effect of domain such that there would be larger deficits in inhibitory control and working memory relative to shifting. While there was a main effect for domain, working memory was not significantly different from shifting when data were collapsed across samples. Results also provided partial support for Hypothesis 3(c), which predicted a significant group by domain interaction such that individuals with HD would exhibit more impairment on inhibitory control relative to other areas of EF, and individuals with MDD would exhibit more impairment on working memory relative to other areas of EF. While the predicted pattern bore out in the HD group, working memory did not emerge the most impacted EF domain in the MDD group.

Finally, as an exploratory aim, multiple models were run to test for interactions between multiple elements of EF and processing speed as predictors of coping. There was no evidence in the

MDD sample that working memory was associated with secondary control coping, nor that inhibitory control moderated this association. Similarly, in the HD sample, there was no evidence from regression models that inhibitory control was associated with secondary control coping, nor that working memory moderated this association. Additional analyses investigating the potential moderating role of processing speed on the link between either working memory (MDD sample) or inhibitory control (HD sample) and secondary control coping also indicated no significant main or interaction effects.

4.2 Clinical Implications

4.2.1 Implications of between and within group differences

There are disease processes in both HD and MDD that affect brain function, and brain regions are not affected at random. Both conditions affect regions important for inhibitory control and regions that subserve the ability to use complex cognitive skills. It is important to investigate additional behavioral consequences of these effects on the brain to inform interventions aimed at addressing negative functional outcomes.

This sample of adults with a history of MDD did not show significant EF deficits, particularly after making a possible score adjustment on the test of inhibitory control. Importantly, these adults were tested during a period when they were remitted from depression (i.e., not currently in episode). Based on these findings, EF impairment in adults with a history of depression does not appear to be an area of concern. However, these results are inconsistent with previous meta-analyses indicating that EF impairments persist following remission (e.g., Semkovska et al., 2019). Some evidence suggests that EF impairments may be exacerbated during periods of high stress, but that these effects are reversible, at least in healthy human subjects (Liston et al., 2009). It is possible that, in the sample of parents with a history of MDD included in this study, deficits had been reversed upon remission.

The lack of observed effects could also indicate that the NIHTB-CB was not sensitive enough to detect EF impairments in this sample. The NIHTB-CB has not been used widely with either of these populations. Our research team reviewed previous studies that used this measure and only identified one study that had used the NIHTB-CB with individuals with MDD (Koopowitz et al., 2021). Several aspects of this single study by Koopowitz and colleagues, however, make it difficult to compare with the present findings. Specifically, the authors did not specify whether the NIHTB-CB was administered on an iPad or on a desktop; the study included only 30 individuals with MDD; and the authors presented raw scores rather than standard scores. However, no significant differences emerged on raw scores between sample with depression relative to controls. The only significant differences that emerged between included samples were on the test of processing speed, but differences are difficult to interpret because raw scores rather than standard scores were used (Koopowitz et al., 2021).

For the MDD sample in the present study, results from the NIHTB-CB did not provide evidence of widespread EF impairment. However, if one takes the FICA score at face value (i.e., without the possible 10-point adjustment), then inhibitory control seems to be both a relative and an absolute deficit. This would suggest that individuals with a history MDD experience persistent impairments in inhibitory control, even out of episode, while other domains of EF are not as affected. It is important to note, though, that it is possible that the FICA score is off by exactly the order of magnitude that would put it right at the normative mean with the 10-point adjustment. Future studies should use additional measures of EF and longitudinal designs to investigate the trajectories of EF performance when individuals are both in and out of depressive episodes.

The sample of patients with HD, however, evidenced significant EF deficits across all domains tested, and these deficits were approximately one standard deviation below the normative mean on all measures (after possibly adjusting 10 points on the FICA test). These results were in line

with expectations and previous work. In contrast to MDD, which is episodic in nature, it is reasonable to expect that because of its non-episodic, progressive course, the stress of HD continues relentlessly, as does patients' impaired ability to manage that stress. EF impairments may be compounded by continuously high levels of stress.

The clinical implications of the findings for the HD sample suggest two potential avenues for helping patients: by dealing directly with their stress management skills or by improving EF skills. Previous work suggests that either of these approaches may be helpful. One empirical study by our research team randomized college students to either a 6-week cognitive training program or a 6-week coping skills intervention and investigated effects on psychosocial stress levels, EF, and symptoms of anxiety and depression (Bettis et al., 2017). A goal of the study was to explore whether that there would be a "top down" effect of teaching coping skills that would in turn improve EF skills or a "bottom up" effect of improving EF that might automatically improve individuals' ability to cope. On the one hand, teaching cognitive coping skills requires practice with engaging and applying EF skills to manage emotional responses. On the other hand, directly improving EF skills may facilitate cognitive coping by increasing the efficiency of cognitive skills required for secondary control coping strategies including cognitive reappraisal. Participants in both conditions reported reduced stress, reduced EF challenges, and reduced anxiety symptoms following the intervention (Bettis et al., 2017). Results suggest that interventions targeted at improving either coping skills or EF skills may be beneficial for individuals with HD.

Further, the Bettis et al. (2017) study was conducted with college students in a health-promoting model and suggests benefits even in the absence of clear psychopathology symptoms. Thus, even while not currently in a depressive episode, parents with a history of MDD may benefit from either of these short-term interventions targeting EF skills or coping. A recent meta-analysis reviewing the state of the evidence supporting the effectiveness of cognitive control training for

individuals with MDD suggested that interventions to improve EFs are a promising line of intervention, but evidence for effectiveness is more modest when levels of depression symptoms are low at baseline (Koster et al., 2017). Thus, potential benefits to patients with MDD who are in remission may also be modest.

Findings from the HD sample indicate that all three core EF domains are targets for intervention in this population. A challenge for interventions aiming to enhance EF is that cognitive training programs provide evidence of "near" but not "far" skill transfer. Results of a study conducted by our research team with pediatric brain tumor survivors provides evidence of near transfer following working memory training such that working memory training translated to improvements in working memory performance on standardized tests (Siciliano et al., 2022). However, while there is evidence that cognitive training can improve performance on the specific domain targeted in the training (e.g., (Nguyen et al., 2019; Siciliano et al., 2022), there is significantly less evidence suggesting that these interventions enhance performance on other aspects of EF (i.e., they do not exhibit far transfer), and little evidence that they improve performance on distantly related tasks or on everyday cognitive tasks (Schwaighofer et al., 2015; Simons et al., 2016). On the other hand, overall EF decline may be attenuated by engagement with practices that support general brain health, such as exercise (Farina et al., 2014; Law et al., 2020), mindfulness meditation (Goldberg et al., 2022), and maintenance of social connection (Davidson & McEwen, 2012).

4.3 Limitations and Future Directions

4.3.1 Limitations

To fully consider the contribution of these findings to existing literature, several caveats should be noted. First, the datasets used in this study are cross-sectional and thus limit my ability to test directionality and draw causal conclusions. Second, while I found evidence for group-level differences in EF performance after controlling for depression symptom level, it is important to

note that no measure of depression symptoms fully captures the influence of depression. That is, while the PHQ-9 and ASEBA scales are empirically derived and validated measures of depression symptoms, they are – like most measures in psychology – fallible. Thus, this finding demonstrates only that the difference between the two groups remains over and above an almost certainly fallible measure of depression. Third, and along similar lines, it is important to note that the tasks from the NIHTB-CB do not line up perfectly with the theoretical components of EF (here, inhibitory control, shifting, and working memory). For example, while the DCCS purports to measure shifting in isolation, it also requires inhibition (e.g., filtering out distractions) and working memory (e.g., holding the sorting rules in mind). As with measures of psychiatric symptoms, it is challenging to capture isolated elements of EF in an entirely pure or exclusive way (Snyder et al., 2015). Finally, as noted above, scores from the NIHTB-CB may reflect a need for renorming based on administration of the tests on the iPad (Brearly et al., 2019). While between-group comparisons were likely less affected by this given the decision to only include scores from tests administered on the iPad platform, within-group differences may have been affected, particularly comparisons that were made in relation to the FICA test.

4.3.2 Future directions: A prototype for comparing EFs across DSM-5-TR disorders

This study adds to existing literature in several ways. First, the study design provides a model for using the same "measurement stick" to assess executive functioning in two neuropsychiatric disorders included in the DSM-5-TR. It demonstrates how researchers can use the RDoC framework to understand behavioral manifestations of neurological differences between multiple disorders. Here, comparisons focused on investigating group differences in cognitive systems (EF) and regulatory systems (emotion regulation and coping), two domains delineated in RDoC. However, there are a multitude of disorders that would make for interesting comparisons, and

particularly those with more overlapping symptoms (e.g., major depressive disorder and generalized anxiety disorder).

In addition, this is one of many studies that has used the NIHTB-CB to assess performance on key EF domains. The NIHTB-CB was developed primarily as a research tool but has been used to assess functioning in a variety of clinical samples with psychiatric and neurological problems (Fox et al., 2022). Benefits of using the NIHTB-CB include its expedient assessment of cognitive domains that are typically assessed using a series of tests normed on different samples and over multiple hours. The tests are easily administered and require less intensive training compared to other neuropsychological test batteries, in part because tests are automatically scored and converted to standard scores. Ultimately, and with updated norms, the NIHTB-CB has the potential to be scaled up for use as a clinical screening tool to assess the need for more comprehensive neuropsychological evaluations in patients at risk for EF challenges.

4.3.3 Future directions: EF, Coping, and Symptoms of Depression

Results from correlation analyses indicated small positive associations between EF domains and use of secondary control coping for the HD group, and associations were also present the shifting and working memory domains in the MDD group. Large negative associations between reported use of secondary control coping and self-reported depression symptoms were present for both groups. The more individuals reported using secondary control coping strategies, the fewer symptoms of depression they had. This robust finding is consistent with broader literature; greater use of engagement coping strategies, such as problem-solving and cognitive reappraisal, is associated with fewer symptoms of depression and anxiety in individuals across the lifespan (Aldao et al., 2010; Compas, Jaser, Bettis, et al., 2017), and suggests an avenue for future investigations to examine the role of EF processes in influencing the link between coping and symptoms of depression.

Meta-analytic evidence suggests that significant EF deficits are present in individuals with both depression (Snyder, 2013), anxiety (Moran, 2016), and posttraumatic stress disorder (Scott et al., 2015). However, associations between EF skills and depression symptoms were not observed in either of the samples tested in this study. There is also evidence to suggest that use of secondary control coping may partially explain the link between EF abilities and anxiety and depression symptoms. The links between working memory and inhibitory control and secondary control coping appear to be particularly important in predicting individual differences in distress. In HD patients, there is evidence to suggest that secondary control coping has an indirect effect on the association between inhibitory control and symptoms of anxiety and depression (Ciriegio et al., 2022). In a study of pediatric brain tumor survivors, use of engagement coping strategies mediated the association between brain activation during a working memory task and symptoms of anxiety and depression, such that greater use of strategies partially explained the link between increased brain activation and fewer symptoms (Robinson et al., 2015). While coping is an important functional outcome associated with reduced distress (Aldao et al., 2010; Compas, Jaser, Bettis, et al., 2017), both HD and MDD portend heightened levels of stress (Ciriegio et al., 2019; Jaser et al., 2005), and both conditions may negatively impact the cognitive capacities necessary to cope with stress. A direction for future research may be to further examine the associations among physiological stress responses, EF skills, secondary control coping, and symptoms of anxiety and depression in samples affected by HD and MDD.

4.3.4 Future directions: Inhibitory control and reward circuitry

Reward circuitry is also implicated in both depression and HD and may affect emotional and behavioral functioning. Reward circuitry and dopaminergic signaling drives motivated behavior because the same brain regions that are activated when one experiences success or pleasure are activated when recalling or thinking about previous successes or pleasurable experiences (Clark &

Dagher, 2014; Steinberg, 2008). Individuals with HD tend to exhibit clinically concerning levels of impulsivity and engage in high-risk behaviors (McDonell et al., 2020). This may be related to disruptions in inhibitory control circuitry that typically serves as a "brake" on impulsive behaviors in cases where risk outweighs reward (Munakata et al., 2011). Individuals affected by depression, however, may demonstrate hyposensitivity to reward, with some evidence suggesting that blunted reward responsivity may underlie anhedonia (e.g., Proudfit et al., 2015).

The task used in this study to assess inhibitory control was emotionally neutral (i.e., a "cool" EF task; Zelazo, 2020; Zelazo & Carlson, 2012) and so reflects inhibitory control skills activated in the absence of heightened emotion. Results from this study indicate that individuals with HD exhibit deficits in inhibitory control even when it is called upon under emotionally neutral conditions. The MDD group also exhibited deficits on inhibitory control, although this deficit disappears after possibly making the 10-point adjustment indicated by the results of previous studies indicating a need for renorming of the NIHTB-CB on the iPad (Brearly et al., 2019). A task for future research is to compare these two populations on a measure of EF skills that also induces emotional arousal and activates motivation circuitry (i.e., a "hot" EF task (Zelazo, 2020)). Patterns of EF performance may look different when tested under "hot" emotional conditions.

4.3.5 Future directions: Compensatory models

While I did not find evidence for an additive or multiplicative effect of second EFs on the association between a primary EF and secondary control coping, this pattern of findings does not rule out the existence of compensatory processes for other outcomes. It is possible that other EFs can compensate for deficits in one domain and support other functional outcomes (e.g., occupational functioning, social connectivity, engagement in healthy behaviors). Testing the potential additive or multiplicative effect of other EFs on the link between a primary EF and other social, affective, or adaptive functioning outcomes is another direction for future research.

Additionally, more research on methods for improving EFs is also needed. It is unclear whether improving performance in one area of EF translates to other domains, or if improvements in one domain facilitate functional outcomes of interest (e.g., coping, independent living skills). In order to more fully investigate the role of compensatory effects, studies would need to use longitudinal designs and model cognitive decline over time as a function of change in multiple EFs. Exploring links between behavioral performance and neural correlates would also help elucidate these processes. Some studies have demonstrated more diffuse neural activation during tasks with high cognitive load among individuals with compromised EFs (e.g., patients with multiple sclerosis, Bonnet et al., 2010; children with ADHD, Ma et al., 2012). However, to ascertain the presence of compensatory processes, studies would need to be designed to determine whether there is more neural activation within domain-specific regions to compensate for deficits in other domains during tasks that present a challenge for EF.

Functional neuroimaging data provides evidence that EFs are instantiated in both common and domain-specific cognitive control networks. A recent meta-analysis synthesizing results from 193 functional neuroimaging studies of more than 2,800 healthy adults provides support for a common activation network with nodes in the prefrontal, dorsal anterior cingulate, and parietal cortices that is activated during a wide range of EF-dependent tasks (Niendam et al., 2012). While tasks examining flexibility (switching), inhibitory control, and working memory all elicited this common pattern of frontal–parietal activation, there were also some unique activation patterns specific to EF domains. Tasks examining flexibility (switching) were associated with additional activation in prefrontal, occipital, and temporal regions. Tasks examining working memory and inhibitory control were associated with additional activation in prefrontal, occipital, temporal, and subcortical areas, including the thalamus, caudate and putamen, with each domain appearing to have a slightly different functional "signature" within these regions (Niendam et al., 2012). These meta-

analytic results provide evidence in support of the model that EFs activate both a superordinate, unitary cognitive control network as well as domain-specific networks spanning prefrontal, occipital, temporal, and subcortical areas.

In MDD, disruptions to fronto-limbic circuitry may be a neural correlate of cognitive impairments underlying emotion-regulation difficulties (Pizzagalli, 2011; Roiser et al., 2012). This has led researchers to propose a "cognitive neuropsychological" model of depression, in which negative information processing biases play both a causal and maintaining role in the development of depression symptoms (Roiser et al., 2012). A better understanding of the links between EF and emotion regulation circuitry, and ways to target treatments to various neurological and psychological "nodes" within these networks will require multimodal assessments incorporating neurocognitive, psychological, and neuroimaging data.

4.4 Conclusion

This study made use of a common methodology and shared metric to make comparisons of EF across two disease groups affected by neuropsychiatric conditions: individuals with HD and individuals with a history of MDD. Employing the same metric to assess EF in populations affected by different DSM-5-TR disorders improves our understanding of disorder- and domain-specific impairments, consistent with the RDoC approach to understanding behavioral manifestations of neurological differences between multiple disorders. Findings indicated that individuals with HD are at risk for impairments equal to or greater than one standard deviation below the normative mean across all three core areas of EF (shifting, inhibitory control, working memory). Individuals with a history of MDD outperformed individuals with HD on all three measures of EF and evidenced much lower risk for EF impairments. Results suggest that individuals with HD may benefit from interventions targeting all core EFs, but that EFs may not be a primary target of intervention for individuals remitted from depression. This study did not find support for EF domains and

processing speed entered simultaneously as predictors of secondary control coping but paves the way for future investigations of other compensatory processes linking patterns of neurocognitive functioning to adaptive cognitive, social, and affective outcomes in these and other populations.

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6 Tables

Table 1.
Descriptive Statistics and Correlations for Study Variables

Group	Variable	n	M	SD	1	2	3	4	5
MDD	1. Dimensional Change Card Sort[a]	105	107.95	17.85	–				
	2. Flanker Inhibitory Control & Attention[a]	105	89.74	11.99	.59**	–			
	3. List Sort Working Memory[a]	105	100.95	14.42	.42**	.18	–		
	4. Pattern Comparison Processing Speed[a]	105	102.80	20.84	.45**	.53**	.21*	–	
	5. Secondary Control Coping Ratio	105	0.23	0.05	.14	.06	.21*	.04	–
	6. Depression symptom level (Z-score) [b]	105	0.03	1.01	-.11	-.12	-.08	-.15	-.44**
HD	1. Dimensional Change Card Sort[a]	82	85.79	19.30	–				
	2. Flanker Inhibitory Control & Attention[a]	82	74.27	13.50	.69**	–			
	3. List Sort Working Memory[a]	82	85.40	17.93	.56**	.63**	–		
	4. Pattern Comparison Processing Speed[a]	82	78.76	23.55	.58**	.67**	.70**	–	
	5. Secondary Control Coping Ratio	82	0.26	0.06	.21	.22*	.23*	.17	–
	6. Depression symptom level (Z-score)[b]	82	-0.04	0.91	-.11	-.01	-.03	.06	-.58**

[a]age-corrected standard scores
[b]Z-scores for the HD sample were computed separately for two different measures, then combined into a single variable. Thus, the mean differs from 0 and the SD differs from 1. Values were also affected slightly by multiple imputation of missing values.
**=p<.01; *=p<.05

Table 2.
Results of multivariate and univariate t-tests.

Group	Variable	Dfn	Dfd	M	95% CI	Test statistic (t or T^2)	p
				Multivariate			
	Hotelling's T^2	3	79	--	--	112.61	p <.001
				Univariate			
HD	Dimensional Change Card Sort	81	--	86.09	[81.87, 90.30]	-6.57	p <.001
	Flanker Inhibitory Control & Attention	81	--	74.54	[71.55, 77.52]	-17.00	p <.001
	List Sort Working Memory	81	--	85.44	[81.49, 89.39]	-7.33	p <.001
				Multivariate			
	Hotelling's T^2	3	102	--	--	74.20	p <.001
				Univariate			
MDD	Dimensional Change Card Sort	104	--	107.95	[104.50, 111.41]	4.57	p <.001
	Flanker Inhibitory Control & Attention	104	--	89.74	[87.42, 92.06]	-8.77	p <.001
	List Sort Working Memory	104	--	100.95	[98.16, 103.74]	0.68	p = .500

Table 3a.

Summary of results from multivariate analysis of variance investigating between-group differences on each executive functioning subtest.

Effect		df(n)	df(d)	*F*	*V*[a]
Multivariate omnibus test		3	183	29.10***	0.32
Post-hoc test	Variable	df(n)	df(d)	*F*	n
Welch ANOVA	Dimensional Change Card Sort	1	167	64.80***	187
Welch ANOVA	Flanker Inhibitory Control	1	163	66.68***	187
Welch ANOVA	List Sort Working Memory	1	153	40.98***	187

* $p < .05$; ** $p < .01$; *** $p < .001$.

[a]Pillai's Trace

Table 3b.

Summary of results from Games-Howell post-hoc tests.

Score	Comparison	*t*	95% CI	result
Dimensional Change Card Sort	MDD vs. HD	-22.16***	[-27.59, -16.72]	MDD>HD
Flanker Inhibitory Control	MDD vs. HD	-15.47***	[-19.22, -11.73]	MDD>HD
List Sort Working Memory	MDD vs. HD	-15.55***	[-20.35, -10.75]	MDD>HD

*** $p < .001$.

Table 4a.

Multivariate and univariate effects from multivariate analysis of covariance investigating between-group differences on each executive functioning subtest while accounting for depression symptom level.

Multivariate Effects		df(n)	df(d)	*F*	*V*[a]
Group		3	182	29.21***	0.32
Depression symptoms		3	182	0.66	0.01
Univariate Effects		**Sum of Squares**		***F***	**df**
Independent Variable	Dependent Variable				
Group	Dimensional Change Card Sort	22609.41		66.40***	1
	Flanker Inhibitory Control	11025.50		68.73***	1
	List Sort Working Memory	11133.18		43.09***	1
Depression symptoms	Dimensional Change Card Sort	657.33		1.93	1
	Flanker Inhibitory Control	186.75		1.16	1
	List Sort Working Memory	118.14		0.46	1

* $p < .05$; ** $p < .01$; *** $p < .001$.

[a]Pillai's Trace

Table 4b.

Summary of post hoc analysis of covariance tests illustrating mean differences in EF test performance between groups after accounting for depression symptom level.

Factor	Dependent Variable	Sum of Squares	df	Mean Square	*F*	η^2	ω^2
Group	DCCS	22498.67	1	22498.67	66.07***	0.26	0.26
	FICA	10983.78	1	10983.78	68.47***	0.27	0.26
	LSWM	11099.38	1	11099.38	42.96***	0.19	0.18
Depression symptoms	DCCS	657.33	1	657.33	1.93	7.66×10^{-3}	3.68×10^{-3}
	FICA	186.75	1	186.75	1.16	4.59×10^{-3}	6.45×10^{-4}
	LSWM	118.14	1	118.14	0.46	2.01×10^{-3}	-2.38×10^{-3}
Residuals	DCCS	62652.91	184	340.50	--	--	--
	FICA	29517.41	184	160.42	--	--	--
	LSWM	47542.34	184	258.38	--	--	--

*** $p < .001$.

Note. DCCS= Dimensional Change Card Sort; FICA= Flanker Inhibitory Control & Attention; LSWM = List Sort Working Memory

Table 4c.
Summary of post hoc pairwise comparisons based on estimated marginal means.

Dependent Variable	Group: MDD		Group: HD		*M* difference[a]	SE	df	*t*	*d*
	Est. Marginal Mean	*SE*	*Est. Marginal Mean*	*SE*					
Dimensional Change Card Sort	107.93	1.80	85.82	2.04	22.11	2.72	184	8.13***	1.20
Flanker Inhibitory Control	89.73	1.24	74.28	1.40	15.45	1.87	184	8.27***	1.22
List Sort Working Memory	100.94	1.57	85.41	1.78	15.53	2.37	184	6.55***	0.97

***$p < .001$. *p*-values are Bonferroni-adjusted.
[a] Comparisons are based on estimated marginal means and were calculated as MDD-HD.

Table 5a.

Summary of main and interaction effects from Mixed Analysis of Variance.

Effect	df(n)	df(d)	*F*	η^2
Main effect: Group	1	185	86.05***	0.24
Main effect: Domain	1.89	348	86.24***	0.14
Group*Domain Interaction	1.89	348	5.30**	0.01

Notes. * $p < .05$; ** $p < .01$; *** $p < .001$.

Table 5b.

Results of one-way ANOVA and pairwise comparisons probing the effect of group on domain (between-group effects).

EF Domain	Effect	n	df(n)	df(d)	*F*
Shifting	Group	187	1	167	64.80***
Inhibitory Control	Group	187	1	163	66.68***
Working Memory	Group	187	1	153	40.98***

EF Domain	*M* difference between groups	SE	df	*t* [a]
Shifting	-22.16	1.95	167	8.05***
Inhibitory Control	-15.47	1.34	163	8.17***
Working Memory	-15.55	1.72	153	6.40***

Notes. * $p < .05$; ** $p < .01$; *** $p < .001$. Welch ANOVAs and Games-Howell post hoc comparisons were performed because there was evidence that homogeneity of variance was violated.

[a] For post-hoc tests, a Bonferroni adjustment was applied.

Table 5c.

Results of one-way ANOVA and pairwise comparisons probing effect of domain on group.

Group	Effect	df(n)	df(d)	*F*
MDD group	EF Domain	2	202	42.80***
HD group	EF Domain	2	157	14.74***

Domain comparison	*M* difference between domains	SE	df	*t* [a]
Shifting vs Inhibitory Control	-15.29	1.35	329	8.01***
Shifting vs Working Memory	-4.10	1.44	359	2.01
Inhibitory Control vs Working Memory	11.18	1.20	360	6.61***

Notes. * $p < .05$; ** $p < .01$; *** $p < .001$. Welch ANOVAs and Games-Howell post hoc comparisons were performed because there was evidence that homogeneity of variance was violated.

[a] For post-hoc tests, a Bonferroni adjustment was applied.

Table 5d.

Pairwise comparisons examining differences in test scores by group.

Post-hoc *t*-tests [a,b]		*M* difference	SE	df	*t*	Interpretation
Group	Score comparison					
MDD	Shifting vs Inhibitory Control	-18.21	1.48	181	8.68***	Shifting > Inhibitory Control
	Shifting vs Working Memory	-7.00	1.58	199	3.13**	Shifting > Working Memory
	Inhibitory Control vs Working Memory	11.21	1.29	201	6.13***	Inhibitory Control < Working Memory
HD	Shifting vs Inhibitory Control	-11.52	1.84	144	4.43***	Shifting > Inhibitory Control
	Shifting vs Working Memory	-0.39	2.06	161	0.13	Shifting = Working Memory
	Inhibitory Control vs Working Memory	11.13	1.75	150	4.49***	Inhibitory Control < Working Memory

Notes. * $p < .05$; ** $p < .01$; *** $p < .001$.

[a] For post-hoc tests, a Bonferroni adjustment was applied. Games-Howell post hoc comparisons were performed because there was evidence that homogeneity of variance was violated.

[b] Paired samples *t*-tests; comparisons are repeated measures within subjects.

Table 6a.

Results of linear model examining the effect of working memory, inhibitory control, and their interaction on secondary control coping engagement in adults with a history of depression.

Variable	*B*	*SE*	*t*	*p*	95% CI
Intercept	$2.25x10^{-1}$	$4.48x10^{-3}$	50.66	$p < .001$	[$2.16x10^{-1}$, $2.34x10^{-1}$]
Working Memory (LSWM)	$4.77x10^{-4}$	$3.14x10^{-4}$	1.52	$p = .13$	[$-1.46\ x10^{-4}$, $1.10x10^{-3}$]
Inhibitory Control (FICA)	$-4.08x10^{-5}$	$3.73x10^{-4}$	-0.11	$p = .91$	[$-7.81x10^{-4}$, $6.99x10^{-4}$]
LSWM*FICA	$2.41x10^{-5}$	$2.98x10^{-5}$	0.81	$p = .42$	[$-3.51x10^{-5}$, $8.33x10^{-5}$]

Note. All predictor variables were mean centered to aid in interpretability.

Table 6b.

Results of linear model examining the effect of inhibitory control, working memory, and their interaction on secondary control coping engagement in adults with Huntington's Disease.

Variable	*B*	*SE*	*t*	*p*	95% CI
Intercept	$2.52x10^{-1}$	$7.36x10^{-3}$	34.18	$p < .001$	[$2.37x10^{-1}$, $2.66x10^{-1}$]
Inhibitory Control (FICA)	$7.17x10^{-4}$	$6.01x10^{-4}$	1.19	$p = .24$	[$-4.79x10^{-4}$, $1.91x10^{-3}$]
Working Memory (LSWM)	$2.55x10^{-4}$	$4.38x10^{-4}$	0.58	$p = .56$	[$-6.17x10^{-4}$, $1.13x10^{-3}$]
FICA*LSWM	$3.16x10^{-5}$	$2.61x10^{-5}$	1.21	$p = .23$	[$-2.03x10^{-5}$, $8.35x10^{-5}$]

Note. All predictor variables were mean centered to aid in interpretability.

Table 6c.

Results of linear model examining the effect of working memory, processing speed, and their interaction on secondary control coping engagement in adults with a history of depression.

Variable	*B*	*SE*	*t*	*p*	95% CI
Intercept	$2.27x10^{-1}$	$4.47x10^{-3}$	50.51	$p < .001$	[$2.17x10^{-1}$, $2.34x10^{-1}$]
Working Memory (LSWM)	$4.27x10^{-4}$	$3.12x10^{-4}$	1.37	$p = .17$	[$-1.91x10^{-4}$, $1.04x10^{-3}$]
Processing Speed (PCPS)	$-5.77x10^{-5}$	$2.21x10^{-4}$	-0.26	$p = .80$	[$-4.96x10^{-4}$, $3.81x10^{-4}$]
LSWM*PCPS	$7.04x10^{-6}$	$1.58x10^{-5}$	0.45	$p = .66$	[$-2.43x10^{-5}$, $3.84x10^{-5}$]

Note. All predictor variables were mean centered to aid in interpretability.

Table 6d.

Results of linear model examining the effect of inhibitory control, processing speed, and their interaction on secondary control coping engagement in adults with Huntington's Disease.

Variable	*B*	*SE*	*t*	*p*	95% CI
Intercept	$2.55x10^{-1}$	$7.54x10^{-3}$	33.83	$p < .001$	$[2.40x10^{-1}, 2.70x10^{-1}]$
Inhibitory Control (FICA)	$8.55x10^{-4}$	$6.40x10^{-4}$	1.34	$p = .19$	$[-4.19x10^{-4}, 2.13x10^{-3}]$
Processing Speed (PCPS)	$1.42x10^{-4}$	$3.78x10^{-4}$	0.38	$p = .71$	$[-6.10x10^{-4}, 8.94x10^{-4}]$
FICA*PCPS	$4.96x10^{-6}$	$1.94x10^{-5}$	0.26	$p = .80$	$[-3.37x10^{-5}, 4.36x10^{-5}]$

Note. All predictor variables were mean centered to aid in interpretability.

7 Figures

Figure 1a.

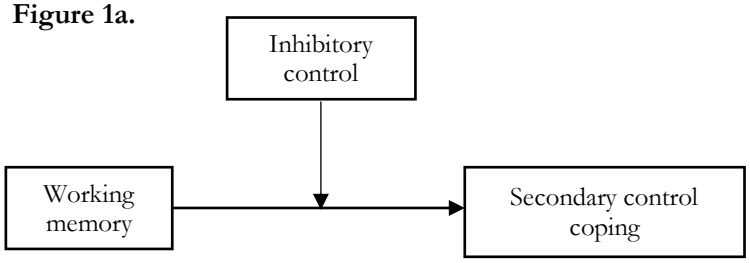

Figure 1b.

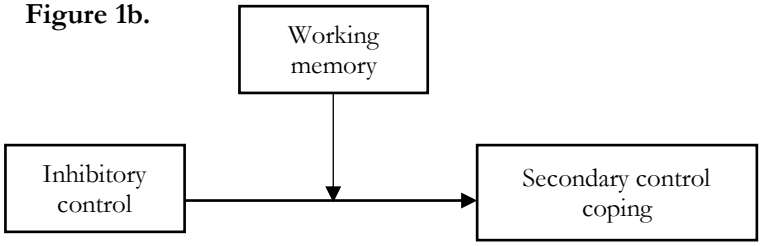

Figure 1c.

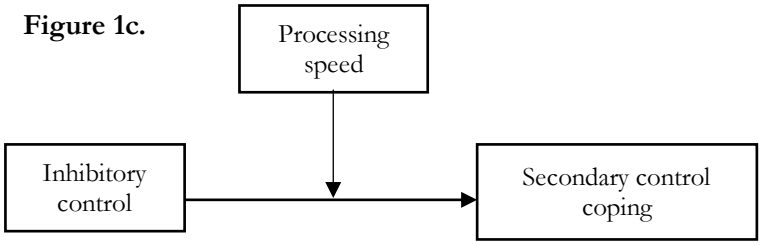

Figure 1d.

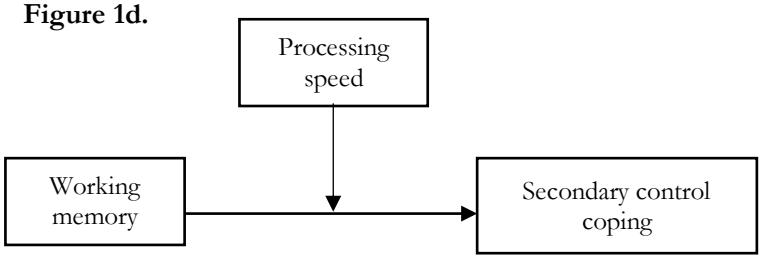

Figure 1a-d. Hypothesized moderation effects. Figures 1a and 1c illustrate hypothesized moderation effects in the MDD sample. Figures 1b and 1d illustrate hypothesized moderation effects in the HD sample.

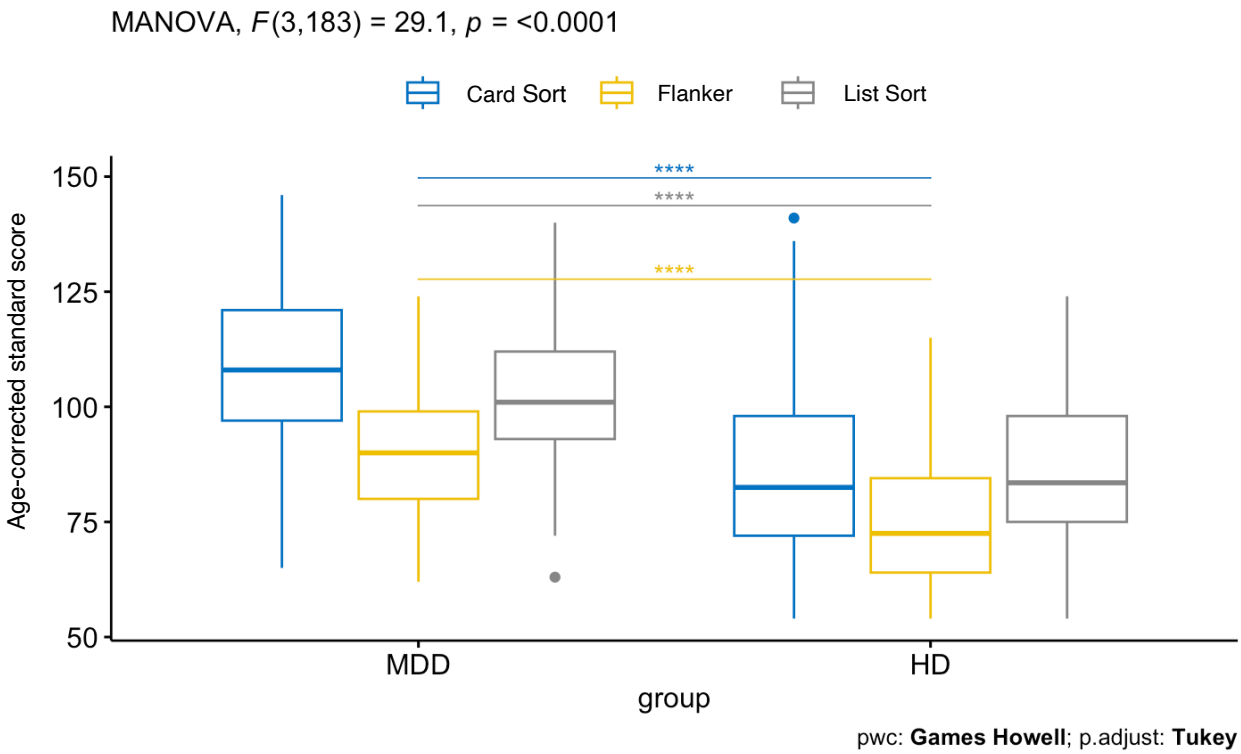

Figure 2. Box plot illustrating mean scores and score distributions on EF subtests for each group.

Figure 3a.

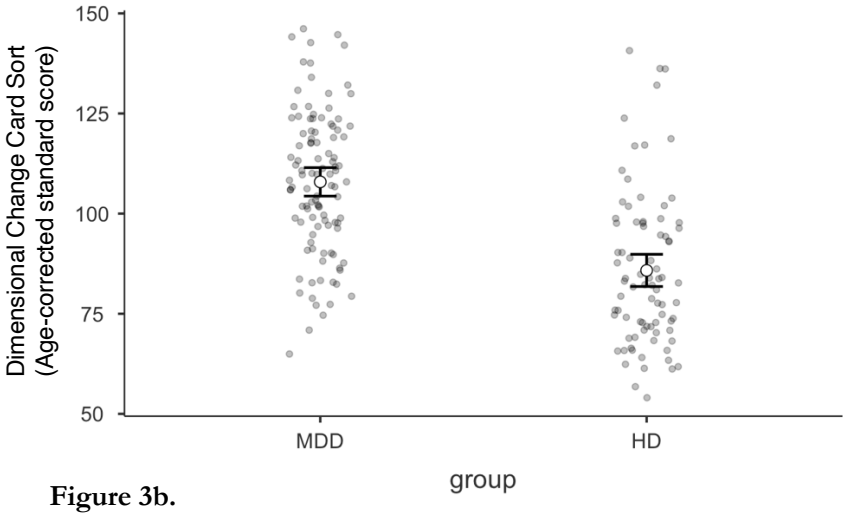

Figure 3b.

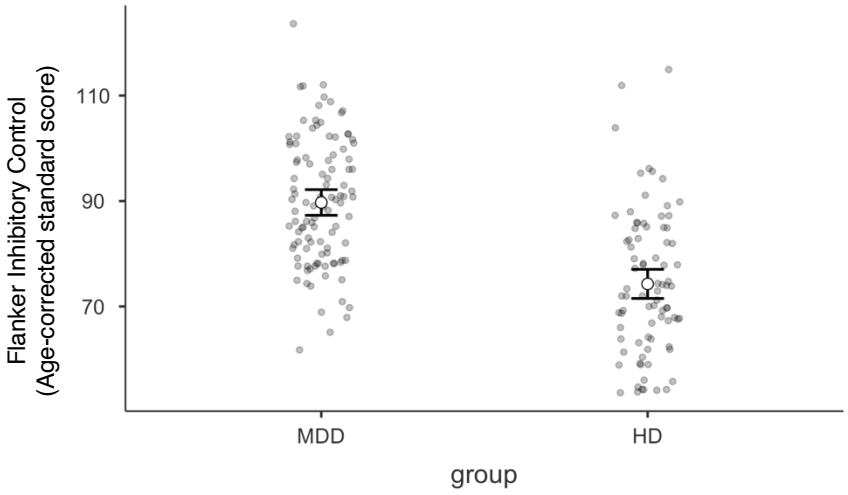

Figure 3c.

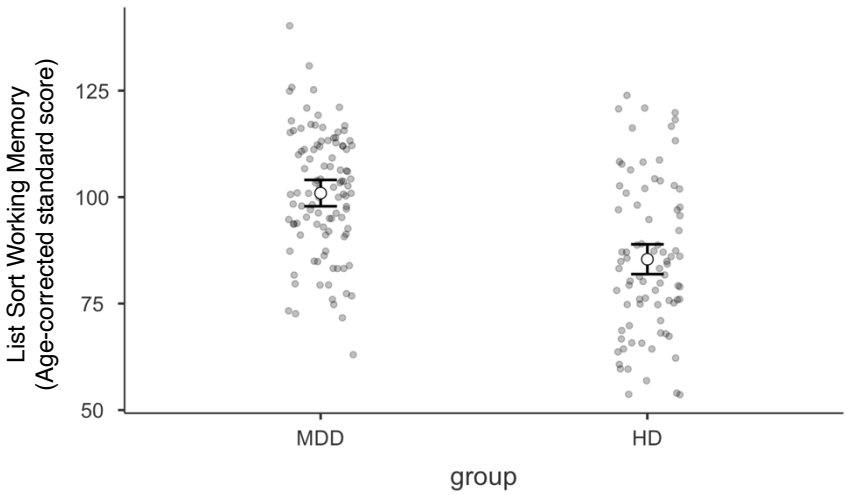

Figure 3a-c. Differences in estimated marginal means for scores on the Dimensional Change Card Sort (3a), Flanker Inhibitory Control & Attention (3b), and List Sort Working Memory (3c) subtests for each group after accounting for depression symptom level.

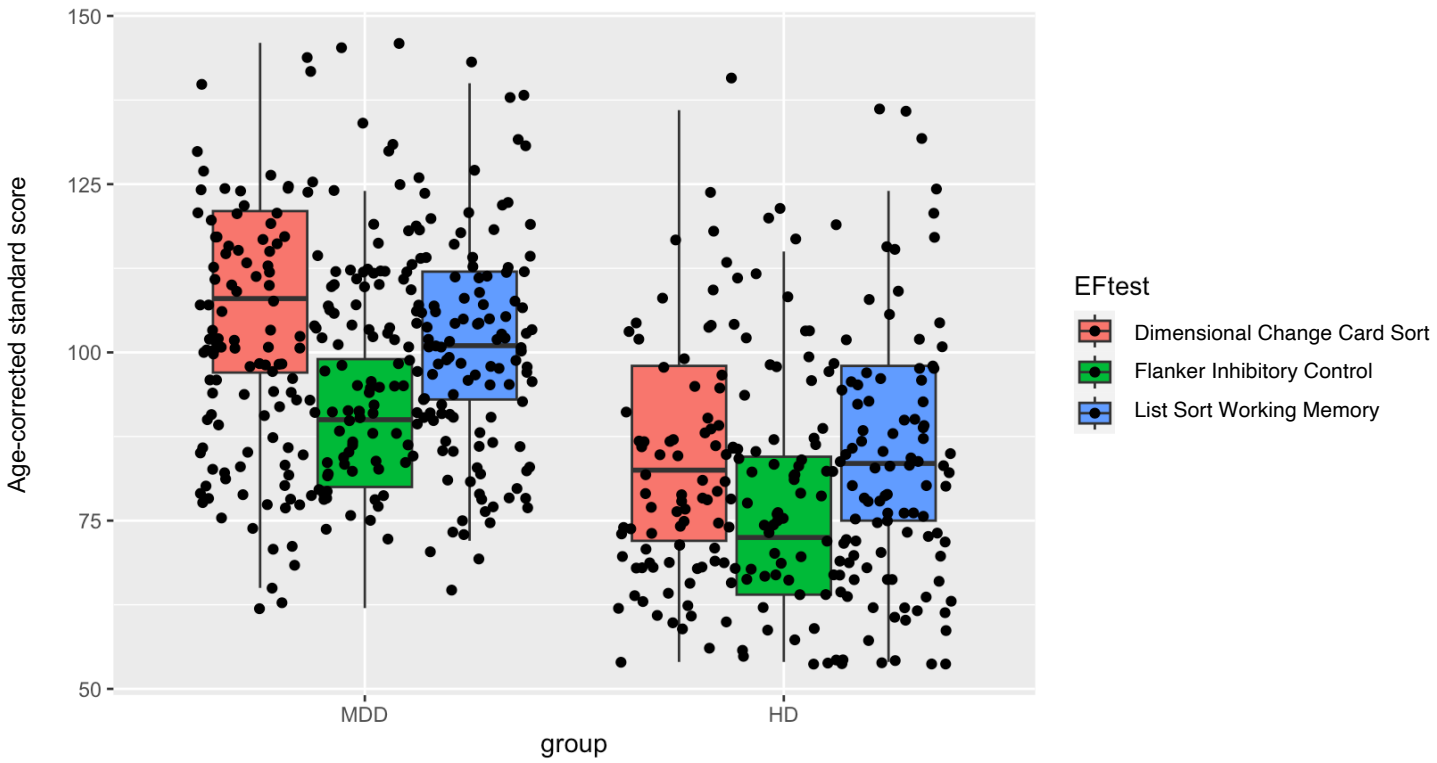

Figure 4. Box and whisker plots illustrating mean scores on the Dimensional Change Card Sort, Flanker Inhibitory Control & Attention, and List Sort Working Memory subtests for each group. Scatters represent individual score distribution.

8 Appendix

I completed a series of tests to examine whether assumptions for analysis of variance family of tests were met prior to conducting the analyses for aims 2 and 3.

Assumptions required for *multivariate analysis of variance* are listed in the table below, along with the test that was performed to check the assumption, whether the assumption was met, and the decision or action step related to that assumption.

Assumption	Test	Met? (y/n)	Result/action step
Adequate sample size	the n in each cell > the number of outcome variables.	Y	As there are 82 and 105 observations per group, the assumption of adequate sample size is satisfied. Proceed
Independence of observations	Each subject should belong to only one group	Y	Proceed
Absence of univariate outliers	Visual check by box plot and by identify_outliers function in R [rstatix package]	Y	There were no univariate extreme outliers in the DCCS, FICA, or LSWM variables, as assessed by box plot methods. Proceed
Absence of multivariate outliers	Compute Mahalanobis distance	Y	There were no multivariate outliers in the data, as assessed by Mahalanobis distance ($p > 0.001$). Proceed
Univariate normality	Check each variable by group with Shapiro Wilk test, then by inspection of QQ plot	Y*	All variables in MDD group were normally distributed as assessed by Shapiro-Wilk's test ($p > 0.05$). For the HD group, LSWM was normally distributed (Shapiro-Wilk's test ($p > 0.05$)), but DCCS and FICA were not (Shapiro-Wilk's test ($p's < 0.05$)). However, QQ plot inspection for these and the other variables indicated that all the points fall approximately along the reference line for each group. **Decision**: Choose to perform the test regardless as MANOVA is fairly robust to deviations from normality and QQ plots look normal. Use Pillai's Trace. Proceed

Multivariate normality	Check multivariate normality with the multivariate Shapiro test	Y	The test is not significant ($p > 0.05$), indicating multivariate normality. Proceed
Identify multicollinearity	Check correlations among DVs (should be moderate but not above 0.9)	Y	All bivariate correlations among DVs are moderate, but not above 0.9, indicating MANOVA is appropriate. Proceed
Linearity	Create a scatterplot matrix for each var by group	Y	There was a linear relationship between test performances in each group, as assessed by scatter plot. Proceed
Homogeneity of covariances	Box's M test	Y	Box's M-test is not statistically significant (i.e., $p > .01$)), so the data have not violated the assumption of homogeneity of variance-covariance matrices. Proceed
Homogeneity of variance	Conduct Levene's test on each EF domain for each group	N	There is homogeneity of variances for DCCS and FICA, but not for LSWM. **Action step**: Do not transform variables but accept a lower alpha level for MANOVA result. Use Pillai's multivariate statistic; use Welch tests and Games-Howell tests for post hoc tests.

Additional assumptions are made for *multivariate analysis of covariance* tests. These assumptions are listed below, along with the test that was performed to check the assumption, whether the assumption was met, and the decision or action step related to that assumption.

Assumption	Test	Met? (y/n)	Result/action step
Linearity	check linearity between covariate and outcome variables	Y	Inspected with scatter plot - associations are linear. Proceed
Homogeneity of regression slopes	Run linear models with interaction term to check for significance	Y	No significant interactions between depression symptoms and grouping variable for any of the dependent variables. Proceed
Normality of residuals	Check plot of residuals	Y	Plots indicate normality.

Homogeneity of covariances	Box's M	Y	Proceed Box's M test for homogeneity of covariances is not significant ($p > .01$)
Multivariate normality	Shapiro-Wilk multivariate normality test	Y	Proceed Shapiro-Wilk multivariate normality test is not significant ($p > 0.05$), indicating normality of residuals.
			Proceed

Additional assumptions are made for mixed model analysis of variance. These assumptions are listed below, along with the test that was performed to check the assumption, whether the assumption was met, and the decision or action step related to that assumption.

Assumption	Test	Met? (y/n)	Result/action step
Absence of univariate outliers	Visual check by box plot and by identify_outliers function in R [rstatix package]	Y	There were no extreme univariate outliers in the DCCS, FICA, or LSWM variables for either group. Proceed
Univariate normality	Shapiro-Wilk normality test Visual inspection of QQ plot	partial	Most scores were normally distributed ($p > 0.05$) for each cell, as assessed by Shapiro-Wilk's test, with two exceptions: HD DCCS score and HD FICA score. However, inspection of the QQ plot is the preferred method when sample size is greater than 50. QQ plots of these two variables indicate normality. **Action step**: Use Pillai's multivariate statistic in later analyses.
Homogeneity of variances	Levene's test	partial	Proceed There was homogeneity of variances, as assessed by Levene's test ($p > 0.05$), for DCCS and FICA, but not LSWM. **Action step**: Adjust post-hoc tests for homogeneity for variances (i.e., use Welch tests and Games-Howell tests.)
Sphericity	Mauchly's test of sphericity [Automatically reported in anova_test]	N	Effect is significant: Eftest: W=0.94; p =.003* Group:EFTest: W=0.94; p =.003*

			Action step: None needed. 'get_anova_table' returns ANOVA table that is automatically corrected for deviation from the sphericity assumption. It applies the Greenhouse-Geisser sphericity correction to within-subject factors violating the sphericity assumption. Thus, reported results are corrected for this violation.
Homogeneity of covariances	Box's M	Y	Proceed Box's M statistic not significant ($p > .01$) Proceed