ANXIETY AND ANHEDONIA IN MAJOR DEPRESSIVE DISORDER:

THE CONTRIBUTING ROLES OF NEUROTICISM,

COGNITIVE CONTROL, AND REWARD LEARNING

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DEDICATION

I would like to thank the members of my dissertation committee for their guidance,

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ANXIETY AND ANHEDONIA IN MAJOR DEPRESSIVE DISORDER: THE CONTRIBUTING ROLES OF NEUROTICISM, COGNITIVE CONTROL, AND REWARD LEARNING

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ABSTRACT

Higher levels of anxiety and higher levels of anhedonia in Major Depressive Disorder (MDD) are two clinical presentations linked to poorer depression treatment outcomes. However, the mechanisms contributing to these symptom presentations remain unclear. Neuroticism, impaired cognitive control, and blunted reward learning have been suggested to be critical processes involved in MDD, and may help to explain symptoms of anxiety and anhedonia.

Using baseline data from individuals with MDD (N=296) in the Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC) study, we conducted a path analysis using structural equation modeling to model hypothesized relationships between the constructs of neuroticism, cognitive control, and reward learning and symptom levels of anxiety and anhedonia. Post-hoc model modifications were performed and relative model fit was compared. Findings indicate that neuroticism was significantly and positively associated with both anhedonia (standardized coefficient = 0.26, $p < .001$) and anxiety (standardized coefficient = 0.40, $p < .001$), whereas cognitive control was significantly and negatively associated with only anxiety (standardized coefficient = -0.18, $p < .05$). Reward learning was not significantly associated with anxiety or anhedonia in the model. These findings suggest that neuroticism may be a potential predisposing factor to both anxiety and anhedonia in MDD, and that cognitive control may be a protective factor to anxiety in MDD. Reducing neuroticism and improving cognitive control through targeted interventions may improve treatment in MDD for those with anxiety and anhedonia.

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LIST OF ABBREVIATIONS

AIC	Akaike information criterion
AMOS	Analysis of Moment Structures
ANH	Anhedonia (latent variable)
ANX	Anxiety (latent variable)
CBT	Cognitive behavioral therapy
CC	Cognitive Control (latent variable)
CFI	Comparative fit index
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EEG	Electroencephalography
EMBARC	Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care
FIML	Full information maximum likelihood
fMRI	Functional magnetic resonance imaging
IQR	Interquartile range
MDD	Major depressive disorder
NE	Neuroticism (latent variable)
NE×CC	Neuroticism × Cognitive Control (latent variable)
NEO-FFI-3	Neuroticism-Extroversion-Openness Five-Factor Inventory-3
PCFI	Parsimony-adjusted comparative fit index
PRT	Probabilistic Reward Task
RB	Response bias
RDoC	Research Domain Criteria

RL	Reward Learning (latent variable)
RMSEA	Root mean square error of approximation
RT	Reaction time
SCID	Structured Clinical Interview for DSM Disorders
SD	Standard deviation
SE	Standard error
SEM	Structural equation modeling
SHAPS	Snaith-Hamilton Pleasure Scale
SPSS	Statistical Package for the Social Sciences
SSRI	Selective serotonin reuptake inhibitor
STAI	State-Trait Anxiety Inventory

Introduction

Major depressive disorder (MDD) is one of the most common and burdensome mental disorders in the United States. In 2014, an estimated 6.7% of all U.S. adults suffered at least one major depressive episode in the past year (Center for Behavioral Health Statistics and Quality, 2015). Individuals with MDD exhibit core symptoms of depressed mood and/or loss of pleasure in nearly all activities, in addition to symptoms that may include feelings of worthlessness or guilt, suicidal ideation, and disturbances in sleep, appetite, energy, concentration, and psychomotor activity. These symptoms are pervasive (i.e., lasting most of the day, nearly every day, for a period of at least two weeks) and are often chronic or recurrent over the lifespan. According to the World Health Organization, MDD carries the heaviest burden of all mental and behavioral disorders, accounting for 3.7% of all U.S. disability-adjusted life years (the total number of years lost to disability) (Murray et al., 2013). Unfortunately, MDD can be difficult to treat due to its often-heterogeneous clinical presentation (Fried & Nesse, 2015), varying in symptom profile and severity from one person to the next. The primary aim of this study is to contribute to efforts to understand this heterogeneity by examining possible psychological mechanisms associated with two common symptom presentations in MDD: anxiety and anhedonia.

Anxiety and Anhedonia Symptoms in MDD

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), one individual with a diagnosis of MDD may exhibit symptoms of feeling hopeless, worthless, restless, and having difficulty sleeping and concentrating because of worry. Yet, another individual with the same diagnosis may exhibit a very different set of symptoms: feeling empty, slowed down, fatigued, eating less, and lacking

enjoyment in life. These disparate symptom profiles – MDD with prominent anxiety and MDD with prominent anhedonia, respectively – are prevalent and associated with not only high depression severity but, perhaps more importantly, poor treatment outcome (Uher et al., 2011). For example, in a large multi-site trial conducted in real-world outpatient settings, 53% of individuals with MDD had high levels of anxiety symptoms, and remission with selective serotonin reuptake inhibitor (SSRI) treatment was significantly less likely to occur in these individuals than in those with non-anxious depression (Fava et al., 2008). Additionally, one study involving depressed outpatients estimated that approximately 37% of individuals with MDD experience clinically significant levels of anhedonia (Pelizza & Ferrari, 2009), and in a trial providing concurrent SSRI and cognitive behavioral therapy (CBT) for treatment-resistant MDD, anhedonia predicted longer time to remission and fewer depression-free days over the course of the trial (McMakin et al., 2012). Indeed, because of their prevalence and contribution to poor treatment outcomes, anxiety and anhedonia appear to be especially important symptom dimensions to examine in MDD.

High levels of anxiety and high levels of anhedonia can be specified as "subtypes" of MDD in the DSM-5 ("with anxious distress" and "with melancholic features," respectively), but these subtypes have failed to guide antidepressant treatment selection (Uher et al., 2011). Similarly, we are not aware of any studies that have shown differential treatment outcome in tailoring behavioral interventions (e.g., CBT) targeted to these symptoms. In addition, individuals often present with overlapping symptom profiles or a subthreshold number of symptoms (Arnow et al., 2015), all of which obscure a precise diagnosis and complicate efforts to target treatment. In a review of depressive subtyping models, Harald & Gordon (2012) recommended that in order to advance the field, subtypes of depression need to move away from

being defined by self-reported symptom clusters and toward causal mechanisms. For example, "heart disease" is currently subcategorized according to underlying mechanism of action (e.g., ischemic, hypertensive causes), and treatment is targeted to causal mechanism, not to symptoms (e.g., chest pain, shortness of breath). In the same way, treatment of "depression" would be improved by targeting causal pathophysiological pathways instead of symptoms (Sharpley & Bitsika, 2013). In order to parse the heterogeneity of MDD and thereby improve treatment precision and clinical outcomes, we need to focus on identifying and understanding mechanisms that cut across current phenotypic symptom categories like "anxiety" and "anhedonia" (Kapur, Phillips, & Insel, 2012).

Symptoms to Mechanisms: Neuroticism, Cognitive Control, and Reward Learning

The Research Domain Criteria (RDoC) initiative by the National Institute of Mental Health is an example of one large-scale effort to identify underlying mechanisms across psychopathology. RDoC aims to build a research construct framework to integrate interdisciplinary research findings at varying levels of analysis (from genes to physiology to self-report), studying the functional domains (e.g., negative valence systems, cognitive systems) underlying the full range of human behavior, from normal to abnormal (Cuthbert, 2014). In this way, psychological constructs can be linked clearly to both biological and behavioral correlates. For example, "working memory" is a proposed RDoC construct that falls under the RDoC functional domain of "cognitive systems," which can be measured and studied on the genetic/molecular level (e.g., dopamine, glutamate) to the circuit/physiological level (e.g., lateral prefrontal cortex) to the behavior/self-report level (e.g., letter-number sequencing task). Along the same lines, previous work in biological psychiatry has employed the concept of endophenotypes – measurable intermediate constructs that bridge phenotype and genotype (Insel

& Cuthbert, 2009). For example, working memory impairment has been proposed as an endophenotype for schizophrenia, a more tractable intermediate construct that bridges symptoms of the syndrome with underlying genes involved in neuronal excitability and prefrontal dopamine expression (Park & Gooding, 2014). According to criteria proposed by Gottesman & Gould (2003), a construct qualifies as an endophenotype for a particular disorder if the construct is (1) associated with the disorder, (2) heritable, (3) primarily state-independent, (4) co-segregated within families, (5) more common in non-affected family members than in the general population, and (6) reliably measured. Fulfillment of these criteria lends support to the genetic basis of endophenotypes. Also, because endophenotypes can be represented as psychological constructs, they may also be amenable to targeted psychological treatments. In a review of potential endophenotypes for MDD, Goldstein & Klein (2014) found good endophenotype criterion support (meeting at least 4 of 6 criteria) for several psychological constructs associated with MDD, including neuroticism, cognitive control, and reward learning, all of which will be examined in the current study.

Using preliminary data from a cohort of patients with MDD (n=82) in the Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC; Trivedi et al., 2016) study, Webb et al. (2016) examined these three constructs – neuroticism (measured by self-report), cognitive control (measured by a behavioral paradigm), and reward learning (measured by a behavioral paradigm). An exploratory cluster analysis of the scores from these measures delineated three statistically distinct subgroups of depressed patients: those with relatively higher neuroticism, those with relatively more impaired cognitive control, and those with relatively more blunted reward learning. In addition, these psychological constructs were found to have partially dissociable neural correlates (as measured by resting-state

electroencephalography [EEG]), reflecting regional differences in underlying resting brain activity among these constructs. Neuroticism was associated with increased ventral anterior cingulate cortex and orbitofrontal cortex activity, impaired cognitive control was associated with decreased left dorsolateral prefrontal cortex activity, and blunted reward learning was associated with decreased orbitofrontal and left dorsolateral prefrontal cortex activity. These resting state differences add to previous research highlighting the neural underpinnings of the psychological constructs of neuroticism (e.g., Bjørnebekk et al., 2013; Ormel, Bastiaansen, et al., 2013; Servaas et al., 2013), cognitive control (e.g., Fassbender, Foxe, & Garavan, 2006; MacDonald, Cohen, Stenger, & Carter, 2000), and reward learning (e.g., Hornak et al., 2004; O'Doherty, 2004; Pizzagalli, Sherwood, Henriques, & Davidson, 2005).

These three constructs also map closely onto important domains in various theoretical models. This includes the RDoC domains of negative valence systems (neuroticism), cognitive systems (cognitive control), and positive valence systems (reward learning), as well as endophenotype models highlighting negative mood bias, impaired cognitive function, and impaired reward function as key biologically-based components of MDD (Hasler, Drevets, Manji, & Charney, 2004). Models of temperament have also outlined similar components linked to the development of psychopathology: negative emotionality (neuroticism), effortful control (cognitive control), and positive emotionality (reward learning) (Snyder et al., 2015). The convergence of evidence suggests that the constructs of neuroticism, cognitive control, and reward learning may represent important mechanisms of dysfunction in MDD. Understanding the contributory role of these constructs to symptoms in MDD ultimately may lead to targeted interventions that have the potential to improve treatment outcomes.

Although each of the constructs of neuroticism, cognitive control, and reward learning has been individually linked to MDD (for a review, see Goldstein & Klein, 2014), we are not aware of any studies to date that have examined them in combination with each other or in relation to specific symptom presentations of MDD, such as anxiety and anhedonia. Miller & Rockstroh (2013) recommend that, due to the complexity and heterogeneity in psychopathology, research efforts should move beyond examining a single causal chain (from genes to symptoms) and toward a multivariate, multilevel approach explicating a network of constructs with well-specified relationships. For example, in a study examining endophenotypes for substance use disorders, two psychophysiological endophenotypes, when considered together, demonstrated added predictive value for identifying risk and also pointed to differences in underlying neural circuits (Iacono, Carlson, & Malone, 2000). Indeed, the RDoC framework consists of such a network of constructs, across different levels of analysis and domains of function. Not only is it important to connect constructs at different levels of analysis *within* each domain, but also it is crucial to connect constructs *between* various domains (i.e., negative valence systems, cognitive systems, positive valence systems), due to the interconnected nature of brain networks and functions. Statistical modeling approaches such as structural equation modeling (SEM) may be especially useful in elucidating such complex networks of psychological constructs involved in psychopathology.

The purpose of the current study is to expand on the results of Webb and colleagues, using the complete EMBARC dataset to examine the associations among the constructs of neuroticism, cognitive control, reward learning, and symptoms of anxiety and anhedonia in a depressed population. We focus on anxiety and anhedonia in MDD due to the prevalence and clinical importance of these symptom profiles, the existing psychometric and neurobiological

evidence suggesting valid distinctions between them (e.g., Clark & Watson, 1991; Sharpley & Bitsika, 2013), and the previous literature pointing to important theoretical and empirical associations between anxiety and anhedonia and the constructs of neuroticism, cognitive control, and reward learning. We will now examine the existing literature, first describing the symptom presentations of anxiety and anhedonia in MDD and the constructs of neuroticism, cognitive control, and reward learning, followed by an integration of the extant evidence and then propose and test a model of how these symptoms and constructs may be connected.

Anxiety in MDD

Anxiety is a common symptom manifestation in MDD. Results from large community and depressed outpatient samples indicate that 12-21% of individuals with MDD concurrently meet symptom criteria for generalized anxiety disorder (Moffitt et al., 2007; Rush et al., 2005), and that about 53% of individuals with MDD also have clinically meaningful levels of anxiety (Fava et al., 2008). With the publication of the DSM-5 in 2013, the specifier "with anxious distress" was added to the formal nomenclature to describe anxious symptoms in MDD, defined as "the presence of at least two of the following symptoms during the majority of days of a major depressive episode: feeling keyed up or tense, feeling unusually restless, difficulty concentrating because of worry, fear that something awful may happen, feeling that the individual might lose control" (American Psychiatric Association, 2013). Definitions of anxiety often emphasize cognitive (worry, lack of control) and somatic (muscle tension, restlessness) components, with anxious states triggered by external stressors or internal cues which are cognitively appraised as threatening (Gros, Antony, Simms, & McCabe, 2007). Uncertainty and anticipation of potential threat tends to lead to frequent and repetitive thoughts characterized by overestimation of risk and consequences, with associated negative emotional and physiological stress responses (Grupe

& Nitschke, 2013). Individuals with anxious symptomology report especially intense and frequent experiences of state anxiety, characterized by negatively valenced thought (e.g., worry) that is often difficult to control.

Anhedonia in MDD

Anhedonia is one of the two core symptoms of MDD, characterized by a diminished interest in previously enjoyed activities. A particularly severe anhedonic symptom presentation is reflected in the DSM-5 with the specifier, "with melancholic features," its core symptom criterion reflecting either complete loss of pleasure in almost all activities, or complete lack of reactivity to pleasurable stimuli (American Psychiatric Association, 2013). According to one estimate, 37% of individuals with MDD experience clinically significant levels of anhedonia (Pelizza & Ferrari, 2009), although some degree of anhedonia is likely present in a much larger proportion of individuals. According to responses to a brief depression screener, 51% of individuals with MDD endorsed anhedonia (as defined by "little interest or pleasure in doing things") "nearly every day," and 76% endorsed anhedonia at least "more than half the days" in the past two weeks (Kroenke, Spitzer, & Williams, 2003). This impairment in capacity for pleasure may reflect dysfunction in neural systems involved in motivation and reward processing. Individuals with anhedonia tend to report decreased emotional and behavioral responsiveness to potentially rewarding environmental stimuli.

Neuroticism

Neuroticism, the propensity to experience negative emotions, is one of the fundamental personality traits according to the five-factor model of personality (McCrae & Costa, 2013). Personality traits, typically measured by self-report, quantify variation in how individuals respond to the environment, with neuroticism characterizing emotional response to threat, loss,

or frustration. (Threat, loss, and "frustrative nonreward" are also RDoC constructs comprising the RDoC domain of negative valence systems.) Higher levels of neuroticism have been correlated with increased amygdala and subgenual anterior cingulate activation during emotional conflict (Haas, Omura, Constable, & Canli, 2007), as well as a distinct pattern of increased subgenual cingulate activity and decreased medial/lateral frontal brain activity under transient stress (Keightley et al., 2003). This suggests that individuals higher in neuroticism may be more sensitive to stressors, reacting with increased negative affectivity and reduced top-down control, which can have adverse physiological and behavioral consequences. Indeed, neuroticism has been shown to be a robust correlate and predictor of both mental and physical health disorders (Lahey, 2009). Individuals with higher neuroticism also demonstrate sustained dorsomedial prefrontal cortex activity with increased connectivity to the amygdala in response to negative emotional facial expressions (Cremers et al., 2010; Haas, Constable, & Canli, 2008), which may reflect the role of increased negative self-referential processing (Northoff et al., 2006). In other words, neuroticism may increase the tendency for negatively valenced, ruminative self-focus in response to negative environmental stimuli.

Large epidemiological studies have shown that neuroticism is significantly predictive of MDD independent of stressful events (Roberts & Kendler, 1999), and that neuroticism and greater adversity significantly increased risk for subsequent depression onset, with neuroticism moderating the effect of stress exposure (Kendler, Kuhn, & Prescott, 2004). In a review of personality factors and depression, Klein, Kotov, & Bufferd (2011) concluded that neuroticism (1) demonstrates moderate-to-large cross-sectional associations with depression, (2) may contribute to subsequent adversity and increased risk of depression in the face of stressful life events, (3) can predict the subsequent onset of depressive disorders, (4) may influence the course

and treatment response of depression, and (5) is related to other forms of psychopathology, particularly anxiety disorders.

Cognitive Control

Cognitive control refers to the degree of ability to regulate thoughts and actions in accordance with internally represented behavioral goals (Braver, 2012). Although there is great diversity in how the broad constructs of self-control or executive function are defined and measured, especially among self-report measures (Duckworth & Kern, 2011), the specific construct of "cognitive control" was defined by an RDoC expert consensus workgroup as "a system that modulates the operation of other cognitive and emotional systems, in the service of goal-directed behavior, when prepotent modes of responding are not adequate to meet the demands of the current context." Components of cognitive control include the ability to monitor performance, inhibit automatic responses in novel contexts, and select appropriate responses (Ridderinkhof, Van Den Wildenberg, Segalowitz, & Carter, 2004). Cognitive control also overlaps with other executive function systems (e.g., attention, working memory) as it is involved in shifting attention and updating working memory in the service of goal-directed behavior. Cognitive control can be operationally defined and quantified by variations in behavioral performance in response to task-interfering incongruent stimuli in paradigms such as the Flanker Task (Eriksen & Eriksen, 1974). Greater cognitive control as measured by scores on behavioral paradigms such as the Stroop or Flanker tasks (Wostmann et al., 2013) have been linked to increased dorsolateral prefrontal cortex activity (e.g., Fassbender, Foxe, & Garavan, 2006; MacDonald, Cohen, Stenger, & Carter, 2000).

Impaired cognitive control has been linked to mood disorders such as MDD. Broad impairments in multiple aspects of cognitive control, especially inhibition and shifting, have

been shown to be reliably associated with MDD, and psychomotor slowing does not account for these results (Snyder, 2013). Longitudinal studies have shown that impairments in updating working memory have been associated with later depression severity (Harvey et al., 2004), and cognitive control deficits have been shown to predate the onset of depressive symptoms (Lee, Hermens, Porter, & Redoblado-Hodge, 2012), persist after remission from depression (Porter et al., 2016; Rock, Roiser, Riedel, & Blackwell, 2014; Vanderhasselt & De Raedt, 2009), and contribute to impairment in psychosocial functioning (McIntyre et al., 2013). Thus, evidence suggests that impaired cognitive control occurs independent of acute depressive state and constitutes a risk factor for the development of depression.

Reward Learning

Reward learning refers to the process by which behavior is modified in response to novel rewards or outcomes, a type of learning by positive reinforcement (Berridge, 2001). Although there are various aspects involved in broader reward and motivational processes, the specific construct of "reward learning," as defined by an RDoC expert consensus workgroup, is "a process by which organisms acquire information about stimuli, actions, and contexts that predict positive outcomes, and by which behavior is modified when a novel reward occurs or outcomes are better than expected." Reward learning has been operationally defined and quantified by variations in behavioral performance bias over time in response to a differential reward, as measured in behavioral paradigms such as the probabilistic reward learning task (PRT), developed by Pizzagalli and colleagues (Pizzagalli, Jahn, & O'Shea, 2005). In other words, individuals who exhibit greater reward learning respond more strongly and selectively to reward cues. Components of reward learning include primary sensitivity to reward as well as ability to learn from reward feedback (Huys, Pizzagalli, Bogdan, & Dayan, 2013). The value that

individuals assign to particular reward cues has been shown to be associated with selective dopamine signaling (Flagel et al., 2011). Blunted reward learning and associated signaling changes could result from reduced exposure to reward cues in the environment over time, or reduced attention or sensitivity to such cues. Reward learning has been shown to be associated with functional connectivity between the amygdala, ventral striatum, and orbitofrontal cortex, which monitors changes in the reward value of stimuli, as well as the dorsolateral prefrontal cortex, which controls attention to such rewards and guides action selection (Hornak et al., 2004).

Blunted reward learning has been associated with MDD. Individuals with MDD exhibit abnormal behavioral responses to both punishments and rewards, which correspond to underlying frontostriatal dysfunction (Eshel & Roiser, 2010). In a longitudinal study, blunted reward learning in depressed patients increased the odds of a persisting diagnosis of MDD (Vrieze et al., 2013). In prospective studies of adolescents, blunted neural response to rewards predicted the onset of major depressive episodes and increase in severity of depressive symptoms (Bress, Foti, Kotov, Klein, & Hajcak, 2013; Morgan, Olino, McMakin, Ryan, & Forbes, 2013).

Reward learning may also be amenable to targeted interventions, for example, psychological treatments such as behavioral activation (Jacobson, Martell, & Dimidjian, 2001) which exposes individuals to rewarding stimuli, extinguishes prediction errors for rewards, and thereby elicits new learning in response to naturally positively valenced stimuli. Relatedly, exposure-based interventions may be particularly suited to target reward learning deficits, as exposure therapies effect change through mechanisms such as inhibitory learning (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014), which may be central to the extinction of

conditioned stimuli-anhedonic responses. Pharmacological interventions specifically targeting dopamine signaling may also directly affect reward learning (Pizzagalli, Evins, et al., 2008).

Present Study

The current study sought to develop and evaluate a model relating the constructs of neuroticism, cognitive control, and reward learning to symptoms of anxiety and anhedonia in MDD, two prevalent and difficult to treat clinical symptom profiles in depression. In particular, this study sought to replicate the previously established association between neuroticism and anxiety, and to examine cognitive control as a potential moderator of this relationship. The study also evaluated the association between neuroticism and anhedonia, and between reward learning and anhedonia. The proposed links between constructs and symptoms comprised a model of interrelationships that were evaluated as a whole. The overarching aim is to further elucidate a mechanistic understanding of anxiety and anhedonia in MDD, using constructs that may suggest targets for more precise intervention.

Neuroticism and Anxiety. Neuroticism may predispose an individual to not only depression but also to symptoms of anxiety. The tendency to experience negative emotions has been found to naturally sensitize individuals to perceived stressors (Hong, 2010). When such stressors involve uncertain or anticipated threat, emotional and/or behavioral dysregulation may result, which may in turn lead to clinical symptoms of uncontrolled worry, tension, and maladaptive avoidance. In large community samples (Jorm et al., 2000; Jylhä & Isometsä, 2006), neuroticism was strongly correlated with both depression and anxiety symptoms and predicted these symptoms three to four years later. In longitudinal studies, individuals high in neuroticism have been shown to be at greater risk for the development and persistence of anxiety symptoms (De Beurs, Beekman, Deeg, Van Dyck, & Van Tilburg, 2000; Schuurmans et al., 2005). A

recently completed three-year longitudinal study concluded that neuroticism prospectively predicted not only first onsets of unipolar mood disorders and anxiety disorders, but predicted even more strongly their comorbidity (Zinbarg et al., 2016). Thus, it is hypothesized that baseline levels of neuroticism will be significantly associated with higher levels of anxiety in MDD.

Cognitive Control and Anxiety. Impaired cognitive control is proposed to be a vulnerability factor in not only depression, but also in a wide range of anxiety-related disorders (De Raedt & Koster, 2010; Mathews & MacLeod, 2005). Anxiety has been linked to deficits in cognitive control processes (Bishop, 2009; Eysenck, Derakshan, Santos, & Calvo, 2007), although the evidence is inconsistent (Paulus, 2015). It is conceivable that anxiety may exacerbate problems in concentration, but it is possible that impaired cognitive control leads to vulnerability to anxiety in the first place.

A recent review of the literature on cognitive control dysfunction in depression and anxiety concluded that there is inconsistent evidence of deficits in cognitive control tasks in individuals with both depression and anxiety (Paulus, 2015). However, individual differences in affective processing and compensatory neural mechanisms may mask behavioral performance deficits (Etkin & Schatzberg, 2011). Evidence suggests that task-irrelevant emotionally valenced processes such as rumination and worry may contribute to whether cognitive control deficits are observed in behavioral performance tasks (Paulus, 2015). Indeed, Gotlib & Joormann (2010) found that when attention was controlled by task demands and there was no opportunity to ruminate, performance deficits in cognitive control tasks disappeared. Rumination and worry are examples of the self-referential and repetitive negative thinking characteristic of individuals high in neuroticism (Muris, Roelofs, Rassin, Franken, & Mayer, 2005; Segerstrom, Tsao, Alden, & Craske, 2000); thus, a possible interactive effect between neuroticism and cognitive control may

be important to examine. Impaired cognitive control may allow irrelevant negative thoughts and images to dominate working memory, leading to difficulty disengaging attention from them (Koster, De Lissnyder, Derakshan, & De Raedt, 2011; Wagner, Schachtzabel, Peikert, & Bar, 2015). This may interfere with emotion regulation (Gotlib & Joormann, 2010; Joormann & Vanderlind, 2014) and contribute to the development of depression and anxiety disorders.

One study examining neuroticism and cognitive control in combination has shown an interactive effect on psychopathological symptoms including depression and anxiety (Muris, 2006). Another study showed that cognitive control moderated the link between negative emotionality and depressed mood, with high levels of neuroticism and low levels of cognitive control resulting in the highest levels of symptoms (Vasey, Harbaugh, Mikolich, Firestone, & Bijttebier, 2013). As such, cognitive control is hypothesized to similarly moderate the relationship between neuroticism and anxiety levels in the current study, and we expect to find that higher levels of cognitive control weaken the relationship between neuroticism and anxiety.

Neuroticism and Anhedonia. Neuroticism is characterized by high negative affect, and anhedonia is characterized by low positive affect. Although negative affect and positive affect have traditionally been considered to be relatively distinct dimensions of emotionality, high negative affect consistently has been found to be moderately correlated with low positive affect (Crawford & Henry, 2004; Tellegen, Watson, & Clark, 1999). This may reflect relative differences in functioning but shared neural circuitry involved in emotional valence (Lindquist, Satpute, Wager, Weber, & Barrett, 2016). Given the association between high negative affect and low positive affect, the personality trait of neuroticism may predispose individuals to not only depression and anxiety, as described earlier, but also to depression with anhedonia. For example, in a sample of patients with chronic depression, anhedonia exhibited trait-like

properties and was significantly correlated with neuroticism (Schrader, 1997). In a 10-year longitudinal study examining the development of depressive and anxiety disorders, the overlap of neuroticism with low positive emotionality prospectively predicted risk of first onset (Kendall et al., 2015). One prospective study in adolescents found that negative emotionality predicted increases in anhedonic depressive symptoms (Wetter & Hankin, 2009). When one's emotional landscape is dominated by negative emotions, positive emotions and rewarding experiences may be less salient, leading to the clinical expression of anhedonia. Thus, we hypothesize that neuroticism will be positively and significantly associated with level of anhedonia.

Reward Learning and Anhedonia. Blunted reward learning is likely a major contributing factor to the clinical expression of anhedonia. An impaired ability to learn from rewarding environmental cues leads to reduced salience of such cues and reduced responsiveness to reward over time. Blunted response to reward feedback information is correlated to self-reported anhedonia in both healthy controls and depressed patients (Steele, Kumar, & Ebmeier, 2007). Vrieze and colleagues (2013) demonstrated that depressed patients with high anhedonia had reduced reward learning compared to patients with low anhedonia, and anhedonia was significantly correlated with depression severity. Blunted reward learning has been correlated with self-reported anhedonic symptoms (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008), prospectively predicts higher levels of anhedonia (Pizzagalli et al., 2005), has been associated with the melancholic subtype of MDD (Fletcher et al., 2015), and endures even in the absence of depression symptoms (Pechtel, Dutra, Goetz, & Pizzagalli, 2013; Weinberg & Shankman, 2017; Whitton et al., 2016). Thus, reward learning is hypothesized to be negatively and significantly associated with anhedonia in the current study.

Hypotheses

To summarize, we propose the following hypotheses that may help in explaining the presence of anxiety and anhedonia symptoms in a depressed population:

1. Neuroticism will be positively and significantly associated with anxiety.
2. The association between neuroticism and anxiety will be moderated by cognitive control, with higher levels of cognitive control weakening this relationship. Cognitive control by itself will not be significantly associated with anxiety.
3. Neuroticism will be positively and significantly associated with anhedonia.
4. Reward learning will be negatively and significantly associated with anhedonia.
5. The hypothesized model comprised of the above interrelationships will be a better fitting model to the observed data, compared to more parsimonious models.

The Hypothesized Model. The hypothesized model depicting all proposed interrelationships is shown in Figure 1. Neuroticism, characterized by negative emotions and a propensity toward negatively valenced self-referential thinking, may lead to both anxiety and anhedonia symptoms in response to stress. Greater cognitive control may specifically help individuals high in neuroticism to counter the effect of this negative self-referential thinking, by decreasing uncontrolled worry and anxiety symptoms. Greater reward learning may contribute to increased experience of positive emotions and reward-seeking behavior, decreasing anhedonia symptoms. By developing and testing a model showing how these three constructs – neuroticism, cognitive control, and reward learning – relate to anxiety and anhedonia symptoms in MDD, we can gain an increased understanding of the possible mechanisms involved in MDD, as well as the comparative importance of each construct, paving the way for more precise interventions targeted to underlying biobehavioral dysfunction. For example, if impaired cognitive control is a

significant moderating factor in the relationship between neuroticism and anxiety, cognitive control training and thought-process focused therapeutic approaches targeting cognitive control deficits may be clinically indicated in the treatment of people with MDD who are high in neuroticism and struggling with anxiety symptoms. If blunted reward learning is a significant contributing factor to anhedonia, exposure-based learning approaches or pharmacological intervention targeting reward learning deficits may be indicated in the treatment of people with MDD with anhedonia symptoms.

Method

Study Overview and Participants

This study is a secondary analysis using baseline data from the Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC) study, a multi-site, placebo-controlled trial of antidepressant treatment response in outpatients with MDD. The primary aim of EMBARC was to examine moderators and mediators of antidepressant treatment response, selected from a broad array of potential biological, behavioral, and clinical markers, and to integrate them in developing a differential depression treatment response index, which will allow better personalization of antidepressant treatment. A two-stage, randomized double-blind design was used, with participants randomized to an initial 8-week trial of sertraline (vs. placebo), with non-responders switched to either bupropion (for sertraline non-responders) or sertraline (for placebo non-responders) for an additional 8 weeks. Additional study details not relevant to this study can be found in Trivedi et al. (2016). Recruiting sites included the University of Texas Southwestern Medical Center, Columbia University, Massachusetts General Hospital, and the University of Michigan. Potential participants were adults exhibiting symptoms of depression and were recruited from the community via advertisements and clinic referrals.

Potential participants were screened for MDD and appropriateness for outpatient care according to inclusion/exclusion criteria described below. Participants underwent the informed consent process following procedures approved by local site Institutional Review Boards. Participants had to agree to, and be eligible for, all study procedures (including fMRI, EEG, blood draws, and psychological testing).

Eligible participants had to meet the following inclusion criteria: (1) age 18-65, (2) meet symptom criteria for a current MDD episode according to the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), and (3) score a total of ≥14 on the Quick Inventory of Depression Symptomology-Self-Report (QIDS-SR). To increase diagnostic accuracy and reduce biological heterogeneity, only participants with early onset (before age 30) and either chronic (episode duration > 2 years) or recurrent MDD (two or more recurrences including current episode) were enrolled.

Exclusion criteria included the following: (1) failure of antidepressant treatment of adequate dose and duration in the current episode, (2) history of inadequate response or poor tolerability of sertraline or bupropion, (3) currently receiving depression-specific psychotherapy (e.g., CBT), (4) current medications with the potential to interfere with study medications (e.g., antipsychotics and mood stabilizers), (5) history of psychosis or bipolar disorder, (6) DSM-IV substance dependence (except for nicotine) in the past 6 months or substance abuse in the past 2 months, (7) other unstable psychiatric or general medical conditions that would require hospitalization or contraindicate study medications, (8) currently pregnant or breastfeeding, (9) clinically significant laboratory abnormalities, or (10) history of epilepsy or anticonvulsant use.

For the current study, all randomized participants in the clinical trial sample (N=296) were included. Prior to randomization (i.e., baseline) and one week after randomization,

participants completed a comprehensive array of self-report, behavioral, and physiological assessments. Participants were antidepressant medication-free for > 3 weeks before completing any baseline measures. This study utilized the baseline data from a selected array of these assessments in order to evaluate depression characteristics in a large medication-free sample. Baseline assessments may have been completed over more than one session, but within a time period of one week. Typically, two sessions were completed during the baseline period: one session for EEG and behavioral paradigm tasks and one session for fMRI procedures, with the order of sessions determined by availability of scheduling at each individual site. During the baseline period, trait self-report measures (e.g., measuring neuroticism) were typically administered first, behavioral tasks (e.g., measuring cognitive control and reward learning) were administered immediately before EEG procedures, and state self-report measures (e.g., measuring anxiety and anhedonia) were administered immediately before fMRI procedures.) Trained and qualified assessors administered all clinical and behavioral measures, following standard procedural manuals across sites.

Measures

Anxiety. The State Anxiety scale of the State-Trait Anxiety Inventory (STAI) (Spielberger, 2010) was used to measure levels of anxiety. We chose to use this measure (vs. other possible anxiety-related symptom subscales collected in EMBARC) because of its greater face validity in assessing cognitive domains of anxiety (e.g., worry) and its greater utility as a continuous variable. The STAI State Anxiety scale consists of 20 items, asking people how they currently feel (e.g., “I feel tense; I feel nervous; I feel worried”) rated on a 4-point intensity scale (from “not at all” to “very much so”). Higher scores indicate greater anxiety, with a possible range of scores from 20 to 80. Although the STAI was designed to differentiate between

temporal fluctuations in anxiety (state) vs. more stable characteristics of anxiety (trait), no significant differences are found between state anxiety and trait anxiety scores in individuals with anxiety and depressive disorders (Kennedy, Schwab, Morris, & Beldia, 2001). Thus, in the current sample of depressed outpatients, state anxiety scores may serve as a proxy for anxious symptoms. Because retrospective self-report of negative mood states tends to be selectively biased (Sato & Kawahara, 2011), momentary assessment of state anxiety may be a more accurate reflection of typical behavioral and emotional responses to uncertainty or anticipation. Indeed, STAI state anxiety has been shown to be strongly correlated with anxiety symptom severity in individuals with major depression ($r = 0.72$; Kennedy, Schwab, Morris, & Beldia, 2001) and has been shown to have validity for measuring anxiety in clinical populations (Oei, Evans, & Crook, 1990). Scores > 52 have been suggested to be clinically significant in patients with mood disorders (Balsamo et al., 2013; Stauder & Kovacs, 2003).

In the EMBARC study, the STAI State Anxiety measure was administered at three time points during baseline data collection (before EEG, before fMRI, after fMRI). Because fMRI procedures tend to act as a stressor provoking uncertainty and anticipation (Katz, Wilson, & Frazer, 1994; Muehlhan, Lueken, Wittchen, & Kirschbaum, 2011), we chose to use the state anxiety score collected before fMRI in our analyses, with the rationale that individuals with higher anxious symptomology would exhibit characteristic levels of state anxiety before the procedure. In a reliability generalization study of the STAI, the state anxiety score demonstrated strong internal consistency (mean $\alpha = 0.91$) and satisfactory test-retest reliability (mean $r = 0.70$), as would be expected for a state/symptom measure (Barnes, Harp, & Jung, 2002). In the current sample, internal consistency for the STAI State Anxiety score was excellent ($\alpha = 0.93$).

Anhedonia. The Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995) was used

to measure levels of anhedonia. The SHAPS is a 14-item self-report scale, with items asking about hedonic experience in the "last few days" for a variety of naturally pleasurable activities, including interest/pastimes, social interaction, sensory experience, and food/drink (e.g., "I would find pleasure in my hobbies and pastimes"). Items consist of four response categories, with "Agree" or "Strongly Agree" responses receiving a score of 0, and "Disagree" or "Strongly Disagree" responses receiving a score of 1. Higher scores indicate higher levels of state anhedonia, with a possible range of scores from 0 to 14, and a score >2 signifying abnormal hedonic tone (Snaith et al., 1995)

In a sample of depressed outpatients, the SHAPS had high internal consistency (α = 0.91), and demonstrated a unidimensional structure with good convergent and discriminant validity as compared to multiple clinician-rated depression measures (Nakonezny, Carmody, Morris, Kurian, & Trivedi, 2010). The SHAPS has shown good construct validity, with theoretically meaningful correlations between other scales representing positive valence and sensitivity for reward, and unrelated to measures of negative affect and sensitivity for punishment (Franken, Rassin, & Muris, 2007). In the EMBARC study, the SHAPS was administered at the same time as the STAI, immediately prior to fMRI scanning during baseline data collection. In the current sample, internal consistency was satisfactory (α = 0.78).

Neuroticism. The NEO-FFI-3 is a 60-item self-report measure assessing the "Big Five" personality traits (12 items per factor) – Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness (McCrae & Costa, 2010). Items corresponding to the Neuroticism factor ask about emotional response tendencies (e.g., "When I'm under a great deal of stress, sometimes I feel like I'm going to pieces."), rated on a 5-point Likert scale ("Strongly Disagree" to "Strongly Agree"), with total scores for each factor ranging from 0 to 48. In an adult sample,

internal consistency for the Neuroticism factor was good ($\alpha = 0.86$); factor structure was well replicated, and the correlation between the obtained factor score for Neuroticism and a priori scale score was 0.96 (McCrae & Costa, 2007). Personality self-report measures such as the NEO have been shown to maintain high reliability and factor structure, even during acute depressive episodes (Costa, Bagby, Herbst, & McCrae, 2005). The Neuroticism score has demonstrated good convergent validity with negative affect across time, as measured by ecological momentary assessment (Miller, Vachon, & Lynam, 2009). In the current sample, the NEO-FFI-3 Neuroticism score exhibited satisfactory internal consistency ($\alpha = 0.74$).

Cognitive Control. A modified version of the Eriksen Flanker Task (Eriksen & Eriksen, 1974; Holmes, Bogdan, & Pizzagalli, 2010) was used to assess cognitive control. Participants were seated at a computer with both hands on the keyboard, presented with a row of arrows on the screen, and were asked to respond as quickly and accurately as possible (via keyboard button press) with the index finger of the hand corresponding to the direction of the center arrow (left or right). The center arrow was presented with adjacent flanking arrows (two on each side), which either pointed in the same direction ('< < < < <,' '> > > > >') (congruent trials) or in the opposite direction of the center arrow ('< < > < <,' '> > < > >') (incongruent trials). Accuracy and reaction time (RT) in milliseconds were both recorded, and interference effects were defined as longer RT and poorer accuracy on incongruent as compared to congruent trials.

A practice block was presented before data collection in order to familiarize participants with the task. Participants completed five blocks of 70 trials (46 congruent, 24 incongruent). To ensure adequate task difficulty, individually titrated response deadlines were established for each block, corresponding to the 85th percentile of the RT distribution from incongruent trials in the preceding block. In each trial, the four flanking arrows were first presented alone for 100 ms, and

then the central arrow was added (50 ms). This stimulus presentation was followed by a fixation cross (1400 ms). To maintain performance at desired levels, a screen reading "TOO SLOW!" was presented (300 ms) if the participant did not respond by the individually titrated response deadline. Also, if participants made < 3 incongruent errors in a block, they were shown "Remember to respond as QUICKLY as possible while still being accurate" and if they made ≥ 6 incongruent errors in a block, they were shown "Remember to respond as ACCURATELY as possible while still being fast." Otherwise, the screen read, "Please respond as quickly and accurately as possible."

Although both accuracy and RT interference effects were computed, we will use the RT interference effect as our primary measure, as RT has been suggested to be more sensitive to cognitive control processes (Prinzmetal, McCool, & Park, 2005). RT interference effects are defined as longer RTs on incongruent vs. congruent trials. Greater interference effects reflect relatively greater deficits in cognitive control, computed as the difference between the mean RT on incongruent trials and the mean RT on congruent trials ($RT_{Incongruent\ trials}$ - $RT_{Congruent\ trials}$), across all five blocks. Interference effects from the Flanker Task have been shown to be a valid behavioral indicator of cognitive control (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999). For consistency across measures (i.e., higher scores represent greater levels of the construct), the RT interference effect variable was reverse scored such that higher scores represent greater levels of cognitive control. The Flanker Task has been shown to induce activation within the anterior cingulate cortex, which is responsible for conflict monitoring and engagement of cognitive control to make behavioral adjustments in response to errors, which is associated with increased activity in the dorsolateral prefrontal cortex (Kerns et al., 2004). The Flanker Task also showed good test-retest reliability (r = 0.80) in adults and good convergent and divergent

validity with other cognitive measures (Weintraub et al., 2013). In the current sample, test-retest reliability over 1 week was assessed, utilizing scores for clinically stable individuals (i.e., 61 non-responders in the placebo arm of the clinical trial), demonstrating acceptable reliability (r = 0.59).

Reward Learning. The Probabilistic Reward Task (PRT; Pizzagalli, Jahn, & O'Shea, 2005) was used to assess reward learning. This paradigm utilizes signal detection theory (Pizzagalli et al., 2005) and a differential reinforcement schedule consisting of a financial reward to induce a response bias over time. Participants were informed that the purpose of the game was to win as much money as possible, but that not every correct response would yield reward feedback. Participants were asked to determine (via keyboard button press) whether one of two stimuli was presented on the computer screen: a short (11.5 mm) or a long (13 mm) mouth, superimposed on a simple cartoon face. Participants completed two blocks of 100 trials. In each trial, a fixation cross was presented for 750-900 ms, followed by a simple mouth-less cartoon face (circle with two dots as eyes) (500 ms), and then joined by a short or long mouth (horizontal line) (100 ms). An asymmetric reinforcement ratio was used, such that correct identification of either the long or short mouth was rewarded ("Correct!! You won 5 cents") three times more frequently ("rich" stimulus) than the other mouth ("lean" stimulus) in each block. The long or short mouth as "rich" stimulus was counterbalanced across participants. Participants were paid a predetermined fixed amount after task completion.

In healthy controls, participants have been shown to develop a response bias (i.e., respond preferentially to the more frequently rewarded stimulus across blocks) (Pizzagalli et al., 2005). A participant's preference for the most frequently rewarded ("rich") stimulus was captured by response bias scores (log β), computed as follows (Pizzagalli et al., 2008):

$$\log \beta = 0.5*\log\{[(Rich_{Correct}+0.5) * (Lean_{Incorrect}+0.5)]/ [(Rich_{Incorrect}+0.5) * (Lean_{Correct}+0.5)]\}.$$

Response bias (log β) scores can range from -1 to 1. Positive response bias scores signify a bias in favor of the more frequently rewarded stimulus, negative response bias scores indicate a bias in favor of the less frequently rewarded stimulus, and a value of 0 signifies the absence of a response bias.

Our main variable of interest is the change in response bias (RB) scores from the first to the second block of trials in the Probabilistic Reward Task ($RB_{Block\ 2} - RB_{Block\ 1}$). The change in response bias scores over time reflects behavioral adjustments in response to selective reward feedback, i.e., reward learning. Lower RB change scores reflect relatively greater deficits in reward learning. All variables were measured on a continuous scale.

Evidence of the validity of the Probabilistic Reward Task response bias as a behavioral indicator for reward learning has been demonstrated in healthy controls and clinical populations (Huys et al., 2013). The Probabilistic Reward Task response bias has been shown to be blunted in individuals with MDD, reflecting impairment at integrating reinforcement history over time, and correlated with self-reported anhedonic symptoms (Pizzagalli et al., 2008). Further, a low-dose dopamine agonist was shown to impair the development of a response bias in healthy individuals, suggesting that phasic dopamine signaling underlie this behavioral measure of reward learning (Pizzagalli, Evins, et al., 2008). One month test-retest reliability of response bias scores has been shown to be adequate (r=.57) in a sample of undergraduate students (Pizzagalli et al., 2005). In the current sample, the test-retest reliability over 1 week was assessed, utilizing scores for clinically stable individuals (i.e., 57 non-responders in the placebo arm of the clinical trial). Test-retest reliability was unexpectedly poor (r = 0.11), which limited the utility of this

measure in the analysis.

Statistical Analysis

Prior to analysis, all observed variables in the model were examined with SPSS for plausible values and outliers, distribution and amount of missing data, and fit between variable distributions and the assumptions of structural equation modeling analysis. Variables examined were the Neuroticism factor score from the NEO-FFI-3 (representing neuroticism), the interference effect on reaction time in the Flanker task (representing cognitive control), change in response bias in the PRT (representing reward learning), the STAI State Anxiety score (representing anxiety), and the SHAPS total score (representing anhedonia). In order to test for a moderating effect, an additional interaction variable (neuroticism × cognitive control) was computed. In order to minimize multicollinearity, the neuroticism and cognitive control variables were mean-centered, and the product of these mean-centered variables was used as the interaction variable. Univariate descriptive statistics were computed to screen for plausible values and univariate outliers ±3 standard deviations from the mean ($z > 3.29$). Outliers were identified via calculation of standardized z scores and visual inspection of histograms and box plots. The assumptions of linearity and homoscedascity were assessed via visual inspection of bivariate scatterplots between all pairs of variables. Normality was assessed via visual inspection of histograms and probability plots, and by evaluating the skewness and kurtosis values (worse the further from 0). Curran et al. (1996) suggest absolute skewness values > 2 or absolute kurtosis values > 7 as thresholds for determining substantial non-normality in large samples (N > 200). Data were evaluated for multivariate normality by assessing for multivariate outliers using Mahalanobis distance, i.e. the distance of a case from the centroid of remaining cases, with $p < .001$. The assumptions of the absence of multicollinearity and singularity (i.e., redundant

variables) were assessed and fulfilled from examining bivariate correlations (variables correlated < .90) and using SPSS collinearity diagnostics (condition index < 30).

SEM procedures were carried out using SPSS AMOS (version 24.0), which builds models in an iterative procedure based on maximum likelihood estimation. Parameters estimated by maximum likelihood are the values that have the largest probability of producing the sample covariance matrix. In the structural equation model, missing data were estimated using the full information maximum likelihood (FIML) method as implemented in SPSS AMOS. This method does not impute missing values but instead analyzes all cases (N=296), using all available data points to compute maximum likelihood estimates of parameters (i.e., the values that are most likely to have resulted in the observed data). FIML outperforms other common data handling methods and is similar in superiority to multiple imputation (Enders & Bandalos, 2001; Roth, 1994). FIML is similar to the expectation-maximization method in that it returns identical parameter estimate values, but improves upon expectation-maximization as it produces unbiased parameter estimates and standard errors for use in structural equation modeling. Sample size in the current study was determined to be sufficient based on rule-of-thumb requirements for SEM analyses: at least 5-10 cases per estimated parameter in the model, and a minimum sample size of 100-200 (Wolf, Harrington, Clark, & Miller, 2013).

Path analysis using SEM was conducted to analyze the hypothesized relationships and to test the theorized model linking the constructs of neuroticism, cognitive control, and reward learning to anxiety and anhedonia in depressed patients (see Figure 1). Because the assumption of no measurement error (when conducting path analysis with “stand-alone” observed variables) is unrealistic, model-based corrections for measurement error were applied by using a latent variable structural equation model to conduct the path analysis (Cole & Preacher, 2014). In this

method, each observed variable serves as a single indicator for a latent variable representing that construct. For each observed variable, the factor loading is set to 1.0, and the error variance is fixed to a value based on a reliability estimate (ρ_{xx}) of that measure: $(1 - \rho_{xx})$ × variance. Thus, each observed variable is represented by a latent variable (in parentheses), which accounts for measurement error. Endogenous variables include the STAI State Anxiety score (ANX) and the SHAPS total score (ANH). Exogeneous variables include the Neuroticism factor score (NE) of the NEO-FFI-3, the interference effect on reaction time in the Flanker task (CC), change in response bias in the PRT (RL), and the mean-centered interaction term: Neuroticism score × Flanker RT interference effect (NE × CC). The reliability of the interaction term (NE × CC) was calculated as a function of the reliabilities of each variable (Busemeyer & Jones, 1983): $[(\rho_{NE} \times \rho_{CC}) + r_{NE\text{-}CC}^2] / (1 + r_{NE\text{-}CC}^2)$. All reliability estimates were obtained using the present study's sample, calculating internal consistency for the self-report measures, and test-retest reliability for the behavioral measures. In this way, measurement error of each observed variable is explicitly specified, and thus the structural model with single-indicator latent variables representing each construct is error-free.

The hypothesized full model (Figure 1) was estimated first. The direction (positive or negative) of the unstandardized path coefficients and their associated *p* values were examined, with $p < .05$ indicating a significant effect. Support for the hypotheses that neuroticism would be significantly and positively associated with both anxiety (H1) and anhedonia (H3) would be evidenced by a significant and positive path coefficient between NE and ANX, and NE and ANH, respectively. Support for the hypothesis that reward learning would be significantly and negatively associated with anhedonia (H4) would be evidenced by a significant and negative path coefficient between RL and ANH. To test the hypothesis that the relationship between

neuroticism and anxiety is moderated by cognitive control, and that greater cognitive control weakens this relationship (H2), we expect that the NE × CC interaction term would be significantly and negatively associated with ANX. The direct path between CC and ANX is included in the full model in order to test the NE × CC interaction term, and we did not expect this direct path to be significant. The magnitudes of the standardized path coefficients were evaluated in order to compare the relative importance of each construct, and the percent of variance in ANX and ANH accounted for by the constructs (as indicated by their squared multiple correlations) are reported. The squared multiple correlation, or R^2, as computed by SPSS AMOS, is calculated as 1 – (the estimated variance of the residual variable divided by the estimated variance of the endogenous variable). For accuracy of model specification, the residuals of ANX and ANH were allowed to correlate in order to indicate their shared unexplained variance (Cole, Ciesla, & Steiger, 2007), as it is likely that anxiety and anhedonia share at least one causal variable that is omitted from the currently specified model. As required in SEM analyses, all exogenous variables were considered free to covary, with covariance between each pair of exogenous variables.

Assessing model fit. In addition to determining the magnitude and statistical significance of the individual connections in the model, we evaluated the overall model fit, i.e., the fit between the covariance matrix of our sample and the estimated population covariance matrix, assessed with several fit indices. To test the hypothesis (H5) that the hypothesized full model (Figure 1) fits the observed data better than more parsimonious models, model fit was assessed, and models were compared and evaluated, as described below. The following indices were chosen based on current recommendations (Hooper, Coughlan, & Mullen, 2008; Hu & Bentler,

1999; Kline, 2015) suggesting these indices are least sensitive to sample size, model misspecification, and parameter estimates.

Absolute fit. Absolute fit measures provide indicators of the fit of a particular model without reference to other models. We examined χ^2 and degrees of freedom (df), with a good fit indicated by a nonsignificant ($p > .05$) χ^2, and a ratio of χ^2 to df less than 3 (Kline, 2015).

Comparative fit indices. Comparative fit indices provide indicators of the fit of a given model compared to a nested model. We examined the comparative fit index (CFI; Bentler, 1990) which compares a model with the independence (null or intercept-only) model: the model that corresponds to completely unrelated variables. CFI values > .95 are indicative of good-fitting models (Hu & Bentler, 1999). We also examined the root mean square error of approximation (RMSEA; Browne, Cudeck, & Bollen, 1993), which estimates lack of fit in a given model compared to the saturated (full or perfect) model: the model with the maximum number of parameters and zero degrees of freedom. RMSEA values of < .06 indicate a good fit (for confirmatory purposes), < .08 is adequate (for exploratory purposes), and values > .10 indicate poor fit (Hu & Bentler, 1999).

Degree of parsimony fit indices. These indices introduce a penalty for complicating the model with too many parameters. We examined the parsimony-adjusted CFI (PCFI), which is the CFI multiplied by the parsimony ratio (*df* of model divided by *df* of independence model). Larger values (closer to 1) are better, with PCFI values > .60 indicating satisfactory parsimony fit. We also examined an information-theoretic fit measure, the Akaike Information Criterion (AIC; Akaike, 1987) which assesses fit with a parsimony adjustment and is used to help choose among several realistic but different models. Small values (as compared to other competing models) indicate good fit.

Model modification. Contingent on the statistical significance of the hypothesized paths between RL and ANH and between NE and ANX, various *a priori* theoretically plausible models (Figures 2 and 3) may be compared to evaluate their relative ability to explain the data (i.e., relative model fit), in the following step-wise fashion. To evaluate the contribution of the interaction effect between neuroticism and cognitive control on anxiety levels, the full model (Figure 1) would be compared to a second model trimming the link between NE × CC and ANX (Figure 2). To assess the unique contribution of cognitive control to model fit, comparisons would be made to a third model further trimming the link between CC and ANX (Figure 3).

If the path between NE × CC and ANX were nonsignificant, this path would be trimmed (Figure 2) and model fit compared. Further, if the path between CC and ANX were nonsignificant, this path would also be trimmed (Figure 3). We expect the paths between RL and ANH and between NE and ANX to remain significant, but if these paths were found to be nonsignificant, empirically based post-hoc model modifications would be conducted. Each model was assessed using the above fit indices, and compared relative to each other using the AIC (for non-nested models). If the difference between a comparison model's AIC is > 10, compared to the AIC of the model with the smallest AIC, the model has little support, and can be omitted from consideration (Burnham, Anderson, & Huyvaert, 2011). If post-hoc model modifications involve nested models, relative model fit could also be compared using chi square difference tests between models. For the chi-square difference test, the chi-square value for the more saturated model is subtracted from chi-square value for the less saturated, nested model. The chi-square difference is then evaluated with degrees of freedom equal to the difference between the degrees of freedom in the two compared models.

Because we do not have an additional sample to cross-validate our models, we compared the correlation between the estimated parameters from the original, hypothesized full model (Figure 1) with the estimated parameters from the final model, using only parameters common to both models. If this correlation is high (>.90), then this indicates that model modifications have not changed the relationships within the model (Tanaka & Huba, 1989), giving us more confidence in the generalizability of the results.

Results

Data Screening

Missing Data. Scores that did not meet quality control standards established in the parent EMBARC study (see Appendix B) in the Flanker Task (n=37, 12.5% of all cases) and PRT (n=32, 10.8% of all cases) were excluded pairwise and treated as missing data. Data from self-report measures were missing in < 1% of all cases, with missing scores from the STAI (n=1), SHAPS (n=1), and NEO-FFI-3 (n=3). Using SPSS missing value analysis, missing data patterns were evaluated, including Little's MCAR test which indicated data to be missing completely at random (MCAR; p = .417), fulfilling assumptions for full information maximum likelihood (FIML) analysis. No imputation procedures for missing data were conducted due to planned FIML analysis, which addresses missing data by using all available data points to estimate model parameters.

SEM Assumptions. Two cases were found to be potential univariate outliers on the Flanker RT interference effect variable (z = 4.42, z = 4.71), and one case was a potential univariate outlier on the PRT change in response bias variable (z = 3.44). However, these case were retained because the observed values were plausible and had little impact on the variable distributions, given the large sample size. Assumptions of linearity and homoscedasticity were

met after visual inspection of pairwise plots. The assumption of normality was met, with all variables exhibiting normal distributions via visual inspection of histograms and probability plots, all skewness values < 2 and kurtosis values < 7. The assumption of multivariate normality was met due to all variables having univariate normal distributions and the absence of multivariate outliers, no cases with Mahalanobis distance $p < .001$. The assumptions of the absence of multicollinearity and singularity were met after inspection of bivariate correlations (all < .90) and condition index < 30 (Belsley, Kuh, & Welsch, 1980). After data screening, all assumptions for SEM analysis were met and all cases were retained, leaving N=296 for analysis.

Sample Characterization

Demographic characteristics are shown in Table 1. The average age of participants was 37 years (*SD* = 13.3), ranging from age 18 to 65, distributed with slight positive skew (skewness = .367, *SE* = .142), with 75% of the sample between the ages of 18 and 48. Female participants represented 66% of the total sample. Sixty percent of participants reported marital status as "single," 20% of participants reported they were divorced, separated, or widowed, and 20% of participants reported they were married. Participants who identified as White and Non-Hispanic represented 52% of the total sample, while 20% identified as African American, 19% identified as Hispanic, 7% identified as Asian, and 8% as "Other." Participants reported a mean of 15 years of education (SD = 2.6), with 43% of participants completing higher education (i.e., beyond high school), 36% of participants with "some higher education," and 21% of participants reporting the highest level of education completed as "high school or less." Regarding economic status, a total of 240 participants disclosed monthly household income, and the median of self-reported monthly household income was $2000 (*IQR* = 3000), with 45% of these participants indicating a monthly household income of greater than $2000, 31% reporting between $1000 and $2000, and

24% reporting a monthly household income of less than $1000 (below poverty). Regarding employment status, 45% of participants reported they were currently not employed, 32% of participants reported working full time, and 24% reported working part time.

Clinical characteristics are shown in Table 2. Over half of participants (53%) endorsed a family history of a serious mental illness (including MDD). The average age of onset of first major depressive episode was 16 years (*SD* = 5.8). For the current major depressive episode, median duration was 15 months (*IQR* = 43) with 66% of "moderate" severity, and 29% of "severe" severity, as determined by the Structured Clinical Interview for DSM disorders. In addition, 114 (39%) of participants exhibited symptoms in the current episode that met criteria for the "with anxious distress" specifier for MDD, as introduced in the DSM-5. The sample was composed of 73% of participants with lifetime major depressive episodes of a chronic nature (episode duration > 2 years) and 27% with episodes of a recurrent nature (mainly euthymic, with 2 or more distinct episodes).

Descriptive statistics for study variables were analyzed for all cases with completed data. In this depressed outpatient sample, 34% of participants endorsed clinically significant levels of anxiety (STAI >52) and 77% exhibited symptoms of anhedonia (SHAPS >2), with 31% meeting these cutoffs for both clinically significant anxiety and anhedonia. Anxiety and anhedonia scores were normally distributed, with a mean score for the STAI of 48.22 (*SD* = 11.54) and a mean score for the SHAPS of 5.59 (*SD* = 3.44). The mean score for Neuroticism from the NEO-FFI-3 was 34.86 (*SD* = 6.48), with scores ranging from 15-48; the mean reaction time interference effect from the Flanker task was 64.19 milliseconds (*SD* = 22.54); and the mean change in response bias score across blocks in the PRT was 0.02 (*SD* = 0.21). The correlation matrix with all observed variables in the model is depicted in Table 3. Significant correlations ($p < .01$) were

found between the scores from the STAI and SHAPS (r = 0.31), Neuroticism and STAI (r = 0.28), Neuroticism and SHAPS (r = 0.20), and between Neuroticism and the Flanker reaction time interference effect (r = 0.22).

Model Estimation

The SEM analysis utilized all cases (N=296), using full information maximum likelihood to handle missing data. The estimated hypothesized full model (Model 1) is depicted in Figure 4, with model fit indices indicating a good fit, $\chi^2(3, 296) = 3.41$, $p = .33$, $\chi^2/df = 1.14$, CFI = .993, RMSEA = .022, AIC = 51.41; however, the model lacks parsimony: PCFI = .142 (see Table 4). Greater neuroticism was associated with increased anxiety (unstandardized coefficient = .797, standardized coefficient = .398, $p < .001$) and increased anhedonia (unstandardized coefficient = .137, standardized coefficient = .250, $p < .01$). Greater cognitive control was independently associated with decreased anxiety (unstandardized coefficient = -.103, standardized coefficient = -.169, $p < .05$). Additionally, there were significant positive correlations between the exogenous variables of neuroticism and cognitive control ($r = .312$, $p < .001$), and also between the disturbances of anxiety and anhedonia ($r = .309$, $p < .001$), indicating that the unexplained variance from anxiety and anhedonia are positively associated. The relationship between anxiety and the neuroticism × cognitive control interaction term was nonsignificant (unstandardized coefficient = .009, standardized coefficient = .089, $p = .239$), as was the relationship between anhedonia and reward learning (unstandardized coefficient = 1.500, standardized coefficient = .035, $p = .860$). All parameter estimates are in Table 5. Because of the nonsignificant path between reward learning and anhedonia, we were not able to make the *a priori* model comparisons as specified in Figure 2 and Figure 3. Instead, post hoc model modifications based on empirical results were performed in an attempt to develop a better fitting, more parsimonious

model. Nonsignificant paths were trimmed one at a time and resulting models were compared.

The path between reward learning and anhedonia was deleted first because it was the path with the smallest (and nonsignificant) standardized coefficient. The trimmed model (Model 2) is depicted in Figure 5 and also fits the data well, $\chi^2(2, 296) = 2.41$, $p = .30$, $\chi^2/df = 1.21$, CFI = .993, RMSEA = .027, PCFI = .132, AIC = 38.41. Parameter estimates are listed in Table 6. Further model modification was pursued, trimming the remaining nonsignificant path between the interaction term (neuroticism × cognitive control) and anxiety, as depicted in Figure 6. This fully trimmed model (Model 3) also fits the data well, $\chi^2(1, 296) = 0.35$, $p = .55$, $\chi^2/df = 0.35$, CFI = 1.000, RMSEA = .000, PCFI = .100, AIC = 26.35. The only exception to good model fit is the poor parsimony fit (PCFI), which penalizes heavily due to the high number of estimated parameters relative to the number of data points. Comparing AIC values, Model 3 has the smallest AIC value, and Model 1 and Model 2 have AIC difference values of > 10 compared to this value. Thus the Model 3 (as depicted in Figure 6) has better relative fit, and Models 1 and 2 can be omitted from consideration. Contrary to our hypotheses, the originally estimated model (Model 1) did not exhibit the best relative fit.

In the final model (Model 3), increased anxiety was predicted by greater neuroticism (unstandardized coefficient = .798, standardized coefficient = .400, $p < .001$) and decreased cognitive control (unstandardized coefficient = -.108, standardized coefficient = -.176, $p < .05$). Hypothesis 1 (that neuroticism will be positively and significantly associated with anxiety) was supported. Hypothesis 2 (that cognitive control would moderate the relationship between neuroticism and anxiety) was not supported. Instead, it was found that cognitive control was negatively and significantly associated with anxiety, in an independent manner. As indicated by the squared multiple correlation (R^2), neuroticism and cognitive control accounted for 14.7% of

the variance in anxiety. In the final model, increased anhedonia was predicted by greater neuroticism (unstandardized coefficient = .140, standardized coefficient = .256, $p < .001$). Thus, Hypothesis 3 (that neuroticism will be positively and significantly associated with anhedonia) was supported. Neuroticism accounted for 6.5% of the variance in anhedonia. The final model did not include the path between reward learning and anhedonia, due to the small and nonsignificant association between these variables. Thus, Hypothesis 4 (that reward learning will be negatively and significantly associated with anhedonia) was not supported. Additionally, it was found that greater neuroticism was associated with greater cognitive control ($r = .312$, $p < .001$), and the unexplained variance in anxiety was positively correlated with the unexplained variance in anhedonia ($r = .301$, $p < .001$). Parameter estimates are listed in Table 7.

Because post hoc model modifications were performed, a correlation was calculated between the parameter estimates from the hypothesized full model (Model 1) and the parameter estimates from the final model (Model 3), $r(11) = 1.000$, $p < .001$, indicating that parameter estimates did not change significantly despite modification of the model, lending increased confidence to the generalizability of results.

Discussion

Using path analysis, we examined how anxiety and anhedonia in MDD may be related to the constructs of neuroticism, cognitive control, and reward learning. The sample of depressed adult outpatients was diverse in terms of age, racial/ethnic identity, and socioeconomic status. Racial/ethnic minorities and individuals with low SES were well represented in the sample, with the study sample being slightly higher than current U.S. census percentage estimates (cf. 16% Hispanic, 13% African American, 5% Asian; 15% below poverty: U.S. Census Bureau, 2010). Almost two-thirds of the sample was female, which is consistent with gender prevalence ratios

for MDD in community samples (cf. 1.7 to 1 female to male ratio: Marcus et al., 2005). Three-fourths of the sample consisted of young to middle age adults (age 18-48). As expected for a study enrolling only participants with chronic or recurrent MDD, participants reported an early age of onset of first major depressive episode and a current episode with long duration and moderate to severe depression severity. In addition, a majority of participants endorsed a family history positive for mental illness. These findings are consistent in describing a representative sample of adult participants with moderate to severe MDD.

The prevalence rates of clinically significant levels of anxiety alone and anhedonia alone in MDD were comparable to previously reported findings, with over one-third of our participants with clinically significant anxiety (cf. 21-29% with comorbid anxiety disorder: Rush et al., 2005) and over three-fourths of our participants with clinically significant anhedonia (cf. 76%: Kroenke et al., 2003). Prevalence rates in the literature may differ based on measurement method and the cutoff used for clinical significance, with some estimates of comorbid anxiety as high as 53-56% (e.g, Fava et al., 2008; Mcintyre et al., 2016). Although anxiety and anhedonia are often regarded as separate entities, the current study showed that anxiety and anhedonia were highly overlapping symptom presentations in MDD. Approximately one-third of participants endorsed *both* clinically significant anxiety and anhedonia, with the majority of clinically significant anxious individuals also endorsing clinically significant anhedonia. This mixed symptom presentation is reflective of what is often observed in clinical practice (Eysenck & Fajkowska, 2017), and underscores the difficulties in targeting treatment when such heterogeneous symptoms are present (*Should we target the anxiety or the anhedonia first?*) and the importance of understanding contributing processes (*Or might there be a common mechanism that leads to both anxiety and anhedonia?*).

As hypothesized, we found that neuroticism was significantly and positively associated with both severity of anxiety and severity of anhedonia. Among all examined relationships, the relationship between neuroticism and anxiety exhibited the largest association, as evidenced by comparison of standardized path coefficients. Contrary to hypotheses, no significant effect of reward learning was found, and no moderating effect of cognitive control was found on the relationship between neuroticism and anxiety. Instead, cognitive control was independently and significantly negatively associated with severity of anxiety. Contrary to our hypothesis, the full model did not exhibit significantly better fit than trimmed models. Although the hypothesized full model (Figure 4) demonstrated good model fit, the final model (Figure 6) trimming all nonsignificant relationships exhibited the best relative fit. In the final model, we also found that the unexplained variances from anxiety and anhedonia were positively correlated, which points to a common cause that was not explicitly modeled in this study. Greater neuroticism was also significantly correlated with greater cognitive control. This positive correlation is contrary to the expectation that neuroticism negatively affects cognitive performance, for example through the mediating role of intrusive thoughts (Munoz, Sliwinski, Smyth, Almeida, & King, 2013). However, it may be that the sensitivity to threat characteristic of neuroticism is associated with greater conflict monitoring (i.e., to detect presence of threats), and thus greater cognitive control task performance (e.g., Prabhakaran, Kraemer, & Thompson-Schill, 2011).

Findings are consistent with prior literature demonstrating an association between neuroticism and clinically significant levels of anxiety, not only in cross-sectional (e.g., Jylhä & Isometsä, 2006) and retrospective longitudinal studies (e.g., Schuurmans et al., 2005), but also in a recently completed prospective (Zinbarg et al., 2016) study predicting first onset of comorbid anxiety and depressive disorders. In a three-year longitudinal study, Zinbarg et al. (2016)

reported that although neuroticism predicted the initial onset of a depressive disorder or anxiety disorder alone, it even more strongly predicted the presence of comorbid depression and anxiety. In the current study, neuroticism was associated with greater anxiety in a currently depressed sample, which lends support to a common process underlying depression and anxiety. Individuals with high neuroticism often report brooding about past events or fretting about the future. Indeed, Webb et al. (2016) reported that neuroticism was associated with increased resting brain activity in ventral anterior cingulate cortex regions, which are implicated in emotional regulation (Etkin, Egner, & Kalisch, 2011) and which are involved in the default mode network (Buckner, Andrews-Hanna, & Schacter, 2008) which is linked to self-referential processing (Northoff et al., 2006) such as rumination and worry. This repetitive negative thinking (i.e., rumination and worry) has been found to characterize neuroticism and is prominent across both depression and anxiety disorders (Olatunji, Naragon-Gainey, & Wolitzky-Taylor, 2013).

Findings also lend support to the association between neuroticism and anhedonia. Neuroticism has been shown to prospectively predict increases in anhedonic symptoms (Wetter & Hankin, 2009). One possible mechanism by which neuroticism affects symptom expression may be through the effects of repetitive negative thinking such as rumination. In non-clinical (Muris et al., 2005) and clinical (Roelofs, Huibers, Peeters, Arntz, & van Os, 2008) samples, rumination was found to mediate the link between neuroticism and symptoms of depression. Longitudinal studies in both never depressed and previously depressed samples (Barnhofer & Chittka, 2010; Mezulis, Priess, & Hyde, 2011) have shown that rumination mediates the link between neuroticism and later depression symptoms. Thus, rumination in individuals with high neuroticism may result in increased focus on the self and decreased focus on the environment,

and this reduced attention to naturally occurring environmental contingencies may lead to clinical anhedonia over time. Individuals high in neuroticism may have an intact ability to learn from reward, but because of ruminative, self-directed negative thinking, they may not be paying attention to potentially rewarding experiences. Indeed, behavioral activation, an efficacious therapy for MDD (Mazzucchelli, Kane, & Rees, 2009), involves "attention to experience" interventions to block ruminative behaviors and maximize exposure to naturally occurring environmental reinforcement (Jacobson et al., 2001).

Although the overlap between anxiety and anhedonia in depressed individuals is commonly observed in clinical practice, the mechanism and temporal sequence of this relationship is unclear. In one large cross-sectional analysis of depressed outpatients, individuals with high levels of anxiety were significantly more likely to endorse items related to anhedonic symptoms such as loss of pleasure/enjoyment (Fava et al., 2004). In several longitudinal studies, anxiety has been found to predict later MDD, including anhedonia symptoms (Moffitt et al., 2007; Parker et al., 1999; Price et al., 2016). In a series of recently completed longitudinal studies (Jordan, Winer, Salem, & Kilgore, 2017; Winer et al., 2017), researchers found that anxiety may lead to depression through anhedonia, such that anxiety-related avoidance leads to loss of pleasure. Conversely, Grillo (2015) posited that anhedonia could lead to depression and anxiety, and in a 10-year longitudinal study, Kendall et al. (2015) found that low positive emotionality characteristic of anhedonia was associated with later onset of anxiety and depressive disorders, but that these effects were largely accounted for by neuroticism. Although neuroticism was associated with both anxiety and anhedonia in the current study, there was a large proportion of variance that was unaccounted for and the unexplained variances of anxiety and anhedonia were correlated. Thus, these two clinical presentations may have common causes

that warrant further studying these symptoms in combination rather than separately as done in the current study.

Contrary to our hypotheses, cognitive control did not moderate the association between neuroticism and anxiety. Rather, there was an independent association, in which higher cognitive control was independently associated with lower levels of anxiety. Although some studies have shown an interactive effect between neuroticism and cognitive control (Muris, 2006; Vasey et al., 2013), these studies utilized self-report measures of cognitive control, compared to the current study, which utilized a behavioral measure. In studies utilizing behavioral measures of cognitive control, impairments in cognitive control have been shown to be independently associated with increased anxiety (De Raedt & Koster, 2010; Paulus, 2015). Using a behavioral measure of cognitive control, one recent longitudinal study showed that impaired cognitive control was independently associated with not only increased depressive symptoms, but also increased anxiety symptoms over 7.5 years (Kertz, Belden, Tillman, & Luby, 2016). Thus, our finding of an independent inverse relationship between cognitive control and anxiety corroborates other studies in which cognitive control is assessed using a behavioral measure (vs. self-report).

Another possible explanation for the absence of the hypothesized interactive effect between neuroticism and cognitive control on anxiety may be due to the restricted range of neuroticism in this sample. Because this sample was comprised of individuals with relatively high levels of neuroticism, the restricted range of neuroticism scores may have attenuated associations involving neuroticism and obscured a possible interactive effect. For example, individuals lower in neuroticism may exhibit less ruminative cognitive processes, and thus cognitive control may have less beneficial effect on these individuals compared to individuals

higher in neuroticism. However, this interactive effect may not have appeared in this study because this sample did not include individuals in the lower range of neuroticism scores. Future studies should examine samples with the full range of neuroticism scores.

Contrary to hypotheses, reward learning was not associated with anhedonia, an association which has been demonstrated in various studies (Pizzagalli, Iosifescu, et al., 2008; Vrieze et al., 2013). Notably, the test-retest reliability of the Probabilistic Reward Task was unexpectedly poor in this sample, which likely affected the ability to detect a relationship. One possible explanation for poor task reliability may be specific to this particular sample, which included individuals with only recurrent or chronic depression, with high levels of depression severity. Pizzagalli et al. (2005) reported that individuals with high depression severity failed to show any changes in response bias across blocks (i.e., reward learning), differing significantly from those individuals with low depression severity. Because the sample in the current study was restricted to individuals with relatively high depression severity, the lack of true variability in reward learning may have led to the low observed reliability in this sample. Future studies examining samples with a wider range of depression severity scores may better elucidate a relationship between reward learning and anhedonia.

It is also possible that other motivationally relevant factors may have had important roles and were not captured in the hypothesized model. Specifically, reward sensitivity and learning rate may be separable components of reward learning that could be important to examine (Huys et al., 2013). Other factors such as perceived control and stress may also significantly affect the relationship between reward systems and anhedonia (Pizzagalli, 2014). In a recent review, Rizvi, Pizzagalli, Sproule, & Kennedy (2016) concluded that based on neuropsychological and neurobiological studies, anhedonia is a multifaceted construct that emphasizes different facets of

hedonic function, including desire, effort/motivation, anticipation, and consummatory pleasure. Because self-report measures like the SHAPS used in this study may only measure one facet of hedonic function, they may not always correlate with reward task performance. Multi-method assessment of anhedonia or examination of specific facets of anhedonia may help to clarify the relationship between reward learning and anhedonia.

In summary, we found that the most parsimonious model explaining anxiety and anhedonia symptoms in MDD consisted of possible mechanistic pathways involving the constructs of neuroticism and cognitive control (see Figure 6). Neuroticism had a significant relationship to both anxiety and anhedonia, signifying that neuroticism is a potential common mechanism that can help to explain symptom presentations with high levels of both anxiety and anhedonia. Further, lower levels of anxiety were associated with greater cognitive control, suggesting the importance of cognitive control as a protective mechanism for clinical anxiety. Neuroticism had a stronger association to anxiety and anhedonia, compared to the contributions of cognitive control and reward learning. These findings not only contribute to the understanding of clinical symptoms and their relationship to psychological constructs, but also suggest possible targets for intervention that may lead to symptom improvement. Although others have posited the importance of cognitive control (e.g., Snyder, Miyake, & Hankin, 2015) and reward learning (e.g., Vrieze et al., 2013) in MDD, targeting treatment to neuroticism may have the greatest relative impact, especially in individuals with high-severity MDD and high levels of both anxiety and anhedonia. Improving cognitive control (e.g., via mindfulness or cognitive control training) may be another independent pathway by which to reduce severity of anxiety in MDD.

Although conceptualized as a trait-like construct, neuroticism is increasingly seen as amenable to change and clinical intervention (for reviews, see: Barlow, Ellard, Sauer-Zavala,

Bullis, & Carl, 2014; Barlow, Sauer-Zavala, Carl, Bullis, & Ellard, 2014). Although inter-individual differences tend to remain stable, people show unique patterns of personality change on an individual level and across the life course (Roberts & Mroczek, 2008). This suggests that levels of neuroticism can be changed. In a placebo-controlled trial, antidepressant treatment with paroxetine had a specific effect on neuroticism that was distinct from its effect on depression symptoms (Tang et al., 2009). A novel "unified" cognitive-behavioral treatment targeting negative emotionality (Barlow, Allen, & Choate, 2004) has also been shown to produce small to moderate effects on neuroticism, which was associated with symptom improvement in a variety of anxiety disorders (Carl, Gallagher, Sauer-Zavala, Bentley, & Barlow, 2014). Cognitive control may also be amenable to change. Targeted cognitive control training (Siegle, Ghinassi, & Thase, 2007) and mindfulness training (Zeidan, Johnson, Diamond, David, & Goolkasian, 2010) have been found to increase cognitive control and ameliorate depressive symptoms. Mindfulness, characterized by nonjudgmental awareness and acceptance of internal thoughts and emotions, has been consistently associated with greater cognitive control (Moore, Gruber, Derose, & Malinowski, 2012), suggesting that increased mindfulness and cognitive control are similar psychological capacities enhancing emotion regulation (Teper, Segal, & Inzlicht, 2013).

Limitations and Future Directions

In this study, we utilized the baseline sample from the rigorously designed EMBARC trial and employed a path analytic approach to examine our hypotheses. This analytic approach utilized a latent variable modeling correction in order to reduce the typical drawback of unaccounted measurement error when observed variables are assumed to be perfectly reliable (Cole & Preacher, 2014). Error reduction and error correction strategies were utilized, which allowed for inclusion of prior knowledge about measurement quality. However, these strategies

also have analytical shortcomings, which include under- or overcorrecting for measurement error due to reliability estimates varying from sample to sample. Future studies using multi-method approaches may improve upon this analysis by using multiple indicator variables to represent latent constructs. With multiple indicator variables representing a latent construct, measurement error would be estimated and removed in the measurement model, instead of the need to fix the error variance based on the reliability estimate, as was done with the one-indicator latent variables in the current study.

In fact, neuroticism, cognitive control, and reward learning may be multifaceted constructs in themselves, and representing these variables as latent constructs may be warranted, in order to better understand underlying mechanisms. For example, the construct of neuroticism reflects not only increased sensitivity to negative emotions, but also deficits in downregulation of negative emotions. Cognitive control can be dissociated into related components of switching, inhibition, and performance monitoring (Miyake et al., 2000), and different behavioral paradigms may emphasize different components of cognitive control. In addition, other important psychological constructs may also be important to examine. For example, constructs associated with neuroticism such as psychological inflexibility, emotion dysregulation, and shame have been hypothesized to mediate the relationship between neuroticism and anxiety (Paulus, Vanwoerden, Norton, & Sharp, 2016). Other constructs such as stress and rumination have been proposed to play mediating roles in the association between cognitive control and psychopathology (Snyder & Hankin, 2016).

Due to the significant correlation between the unexplained variances of anxiety and anhedonia, extraneous variables that were not included in the model may have even more explanatory power in explaining symptoms of anxiety and anhedonia. For example, other outside

factors (e.g., environmental stress) or psychological factors (e.g., rumination) may be moderating variables that were not modeled in the current study. Because of the sample characteristics (high neuroticism, moderate to severe depression), restricted range in these variables may have attenuated some of the hypothesized relationships. Future studies would benefit from expanding the scope of study to participants with a greater range in symptom severity, including those with milder symptoms.

Because this was a cross-sectional analysis in a currently depressed sample, we cannot make any causal conclusions without experimental and longitudinal data. It is possible that clinical symptoms may exhibit a bidirectional effect on neuroticism and cognitive control, which was not modeled in the current study. The SEM analysis conducted in the current study assumes that exogenous variables are not caused by endogenous variables, and that the error variances of endogenous variables are unrelated to exogenous variables. Thus, SEM assumes the modeled system is in a steady state and that the basic causal structure does not change over time, making it difficult to model feedback loops that may be present in the maintenance of psychopathology. Future studies involving other environmental and biological variables, as well as assessing these relationships prospectively and longitudinally in other samples, will be important to further evaluate these findings. For example, a prospective study could be designed with a high-risk sample (i.e., individuals who do not currently exhibit clinical-level depression symptoms but who may have a family history or live in high-stress environments), assessing baseline levels of neuroticism and cognitive control, and at a later time point, measuring symptom levels of anxiety and anhedonia. Ideally, this longitudinal design would also capture individuals with a wide range of neuroticism scores and help to generalize the findings of the current sample to non-depressed individuals. Possible influencing variables such as repetitive negative thinking, perceived stress,

or neural correlates related to neuroticism and cognitive control could be measured and included in the model, to better understand how these mechanistic pathways may work.

Due to the complex relationships among constructs and symptoms involved in psychopathology, alternative conceptual and statistical approaches such as network analysis may also be useful to examine these relationships. Network analysis approaches the symptoms of psychopathology from a causal systems perspective, which describes the possibility that symptoms (such as anxiety and anhedonia) directly influence and interact with each other, and that this system can explain the comorbidity of "mental disorders" (Borsboom & Cramer, 2013). This "causal systems" perspective contrasts with the traditional "common cause" perspective: the conceptualization that symptoms are reflective of underlying common causes (e.g., Caspi et al., 2014), as assumed in the current study. For example, in a network analysis of symptoms in MDD and generalized anxiety disorder, anhedonia and sad mood were found to be connected to feeling anxious via other symptoms of guilt and worry (Beard et al., 2016), suggesting symptoms to target which are centrally important to the network. Indeed, cognitive-behavioral models of psychopathology (e.g., Hofmann, 2014) informally incorporate this complex causal network approach describing how symptoms are maintained, which guides clinical case conceptualization and treatment (Kuyken, Padesky, & Dudley, 2008). Future efforts to elucidate mechanisms involved in psychopathology may benefit from integrating both the common cause and causal systems perspectives, as there are likely to be symptoms within a network that not only covary due to a common cause, but are also causally related to other symptoms.

Conclusion

Individuals with MDD have heterogeneous clinical presentations, in which high levels of anxiety and anhedonia are prevalent and impairing. In a large outpatient MDD sample,

neuroticism was significantly associated with higher anxiety and anhedonia, and cognitive control was significantly associated with lower anxiety. The best fitting model did not suggest an interactive effect between neuroticism and cognitive control, or a significant effect of reward learning. Findings suggest that reducing neuroticism and improving cognitive control may be important processes to target in treatment of MDD.

Table 1

Demographic characteristics (N=296)

	M (SD) or *n* (%)
Age, years	37.1 (13.3)
Female	194 (66%)
Race/ethnicity[1]	
White, Non-Hispanic	155 (52%)
Hispanic	55 (19%)
African American	58 (20%)
Asian	21 (7%)
Other	23 (8%)
Marital status (n=293)	
Single	175 (60%)
Married	58 (20%)
Divorced/Separated/Widowed	59 (20%)
Employment status (n=292) [2]	
Full time	92 (32%)
Part time	70 (24%)
Not Employed	130 (45%)
Education level (n=292)	
Completed Higher Education	127 (43%)
Some Higher Education	104 (36%)
No Higher Education (High school or less)	61 (21%)
Monthly Household Income level (n=240)	
>$2000	107 (45%)
$1000-2000	75 (31%)
<$1000 (Below poverty)	58 (24%)

[1]Percentages sum to greater than 100% because participants reporting Hispanic ethnicity may be of any race and are therefore counted under more than one category.
[2]Percentages are calculated based on non-missing data and do not sum to 100% due to rounding.

Table 2

Clinical characteristics (N=296)

	M (SD) or *n* (%)[1]
Family history (*n*=293), first degree relatives with:	
Serious mental illness	158 (53%)
Depressed mood ≥ 2 weeks	186 (63%)
Age of onset of first Major Depressive Episode (MDE), years	16.3 (5.8)
Lifetime MDE Characterization	
Chronic (episode duration > 2 years)	215 (73%)
Recurrent (mainly well, with 2+ distinct episodes)	81 (27%)
MDE Characteristics	
Duration of current MDE, months[2]	15 (43)
Severity of Current MDE[3]	
Mild	14 (5%)
Moderate	194 (66%)
Severe	87 (29%)
"With anxious distress" specifier in current MDE	114 (39%)
Severity of "anxious distress" (*n*=114)	
Mild	30 (26%)
Moderate	46 (40%)
Moderate-Severe to Severe	38 (33%)

[1]Numbers (%) may not add up to N=296 due to missing data. Percentages are based on non-missing data and may not add up to 100% due to rounding error.
[2]Due to severely positive skewed distribution, median (IQR) is reported instead of mean (SD).
[3]Severity levels were determined by clinical ratings according to the Structured Clinical Interview for DSM disorders (SCID).

Table 3

Pearson correlations, means, and standard deviations of observed variables

Variable	1	2	3	4	5	6	***M***	***SD***
1. STAI-S	--						48.22	11.54
2. SHAPS	0.31*	--					5.59	3.44
3. NEO-N	0.28*	0.20*	--				34.86	6.48
4. Flanker RT	-0.05	0.02	0.22*	--			64.19	22.54
5. PRT ΔRB	-0.02	0.03	0.06	-0.01	--		0.02	0.21
6. NEO-N × Flanker RT	0.04	-0.09	-0.21	0.04	0.04	--	32.18	146.02

* $p < .01$
Pearson correlation coefficient was calculated for each pair of variables for which data was available (cases excluded pairwise)

STAI-S: State-Trait Anxiety Inventory, State Anxiety, n=295; SHAPS: Snaith-Hamilton Pleasure Scale, n=295; NEO-N: NEO-FFI-3 Neuroticism, n=293; Flanker RT = Flanker Task reaction time interference effect, milliseconds, n=264; PRT: Probabilistic Reward Task, change in response bias, log β, n=259; NEO-N×Flanker RT = mean-centered interaction term (product of mean-centered NEO-N and mean-centered Flanker RT), n=262

Table 4

Goodness-of-fit indicators of compared models

Model	χ^2	*df*	χ^2/df	CFI	RMSEA	PCFI	AIC
Model 1	3.41*	3	1.14	.993	.022	.142	51.41
Model 2	2.41*	2	1.21	.993	.027	.132	38.41
Model 3	.35*	1	0.35	1.000	.000	.100	26.35

* $p > .05$ (nonsignificant values indicate good model fit)
CFI = comparative fit index (benchmark: > .95); RMSEA = root mean square error of approximation (benchmark: < .06); PCFI = parsimony-adjusted comparative fit index (benchmark > .60); AIC = Akaike Information Criterion (smaller values indicate better relative model fit)

Table 5.

Parameter estimates for Model 1

Parameter	Standardized estimate	Unstandardized estimate	SE	*p*
Regression Weights				
NE → ANX	.398	.797	.151	**< .001**
NE → ANH	.250	.137	.046	**.003**
CC → ANX	-.169	-.103	.049	**.035**
NE×CC → ANX	.089	.009	.007	.239
RL → ANH	.035	1.500	8.530	.860
Covariances				
NE ←→ CC	.312	31.508	9.136	**< .001**
NE ←→ NE×CC	-.039	-25.174	58.184	.665
NE ←→ RL	.176	.069	.084	.412
CC ←→ NE×CC	-.066	-139.538	203.127	.492
CC ←→ RL	.041	.053	.303	.861
NE×CC ←→ RL	.115	.936	1.979	.636
dANX ←→ dANH	.309	9.296	2.263	**< .001**
Variances				
NE	---	30.803	3.459	**< .001**
CC	---	330.367	44.140	**< .001**
NE×CC	---	1331.147	1858.984	**< .001**
RL	---	.005	.004	.196
dANX	---	104.591	10.241	**< .001**
dANH	---	8.637	.950	**.001**
Intercepts				
NEO-N	---	34.868	.378	**< .001**
Flanker RT	---	64.338	1.383	**< .001**
NEO-N×Flanker RT	---	32.611	9.015	**< .001**
PRT ΔRB	---	.023	.013	.079
STAI-S	---	48.218	.672	**< .001**
SHAPS	---	5.585	.201	**< .001**

Bolded indicates $p < .05$
SE = standard error; NE = Neuroticism; ANX = Anxiety; ANH = Anhedonia; CC = Cognitive Control; NE×CC = Neuroticism × Cognitive Control (interaction term); RL = Reward Learning; dANX = disturbance of ANX; dANH = disturbance of ANH; NEO-N: NEO-FFI-3 Neuroticism score; Flanker RT = Flanker Task reaction time interference effect, milliseconds; PRT ΔRB: Probabilistic Reward Task, change in response bias, log β; NEO-N×Flanker RT = mean-centered interaction term (product of mean-centered NEO-N and mean-centered Flanker)

Table 6

Parameter estimates for Model 2.

Parameter	Standardized estimate	Unstandardized estimate	SE	*p*
Regression Weights				
NE → ANX	.400	.801	.151	**< .001**
NE → ANH	.256	.140	.042	**< .001**
CC → ANX	-.170	-.104	.049	**.034**
NE×CC → ANX	.090	.009	.007	.232
Covariances				
NE ←→ CC	.312	31.516	9.137	**< .001**
NE ←→ NE×CC	-.039	-25.289	58.176	.664
CC ←→ NE×CC	-.066	-139.353	203.128	.493
dANX ←→ dANH	.309	9.268	2.261	**< .001**
Variances				
NE	---	30.817	3.460	**< .001**
CC	---	330.372	44.140	**< .001**
NE×CC	---	1331.088	1858.980	**< .001**
dANX	---	104.361	10.232	**< .001**
dANH	---	8.644	.944	**< .001**
Intercepts				
NEO-N	---	34.873	.378	**< .001**
Flanker RT	---	64.337	1.383	**< .001**
NEO-N×Flanker RT	---	32.663	9.016	**< .001**
STAI-S	---	48.218	.672	**< .001**
SHAPS	---	5.585	.201	**< .001**

Bolded indicates $p < .05$
SE = standard error; NE = Neuroticism; ANX = Anxiety; ANH = Anhedonia; CC = Cognitive Control; NE×CC = Neuroticism × Cognitive Control (interaction term); dANX = disturbance of ANX; dANH = disturbance of ANH; NEO-N: NEO-FFI-3 Neuroticism score; Flanker RT = Flanker Task reaction time interference effect, milliseconds; NEO-N×Flanker RT = mean-centered interaction term (product of mean-centered NEO-N and mean-centered Flanker)

Table 7

Parameter estimates for Model 3

Parameter	Standardized estimate	Unstandardized estimate	SE	*p*
Regression Weights				
NE → ANX	.400	.798	.151	**< .001**
NE → ANH	.256	.140	.042	**< .001**
CC → ANX	-.176	-.108	.049	**.028**
Covariances				
NE ←→ CC	.312	31.515	9.137	**< .001**
dANX ←→ dANH	.301	9.056	2.260	**< .001**
Variances				
NE	---	30.821	3.461	**< .001**
CC	---	330.367	44.140	**< .001**
dANX	---	104.961	10.228	**< .001**
dANH	---	8.648	.944	**< .001**
Intercepts				
NEO-N	---	34.873	.378	**< .001**
Flanker RT	---	64.337	1.383	**< .001**
STAI-S	---	48.218	.671	**< .001**
SHAPS	---	5.585	.201	**< .001**

Bolded indicates $p < .05$
SE = standard error; NE = Neuroticism; ANX = Anxiety; ANH = Anhedonia; CC = Cognitive Control; dANX = disturbance of ANX; dANH = disturbance of ANH; NEO-N: NEO-FFI-3 Neuroticism score; Flanker RT = Flanker Task reaction time interference effect, milliseconds

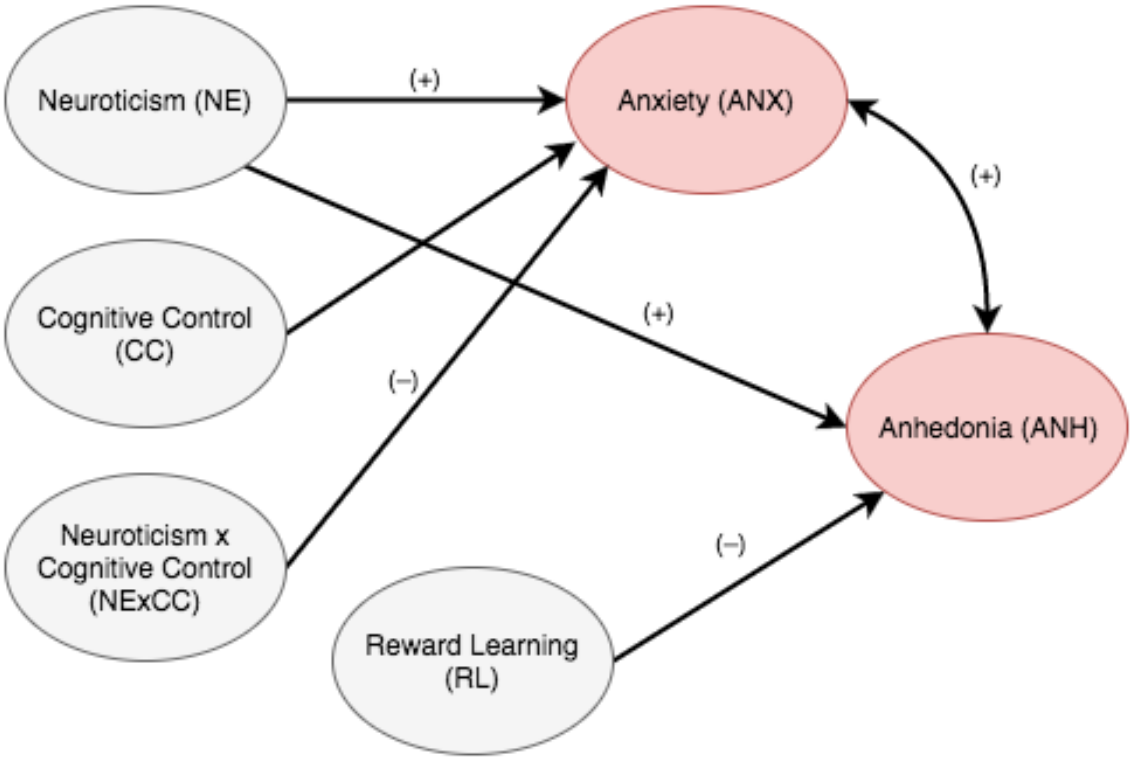

Figure 1. Hypothesized full model. Exogenous variables are shaded grey and endogenous variables are shaded red. The (+) or (–) signs indicate the hypothesized direction of the path coefficient; each are hypothesized to reach significance at $p < .05$. The curved double-headed arrow indicates correlated disturbances. All exogenous variables were allowed to freely correlate, and are not depicted in this figure.

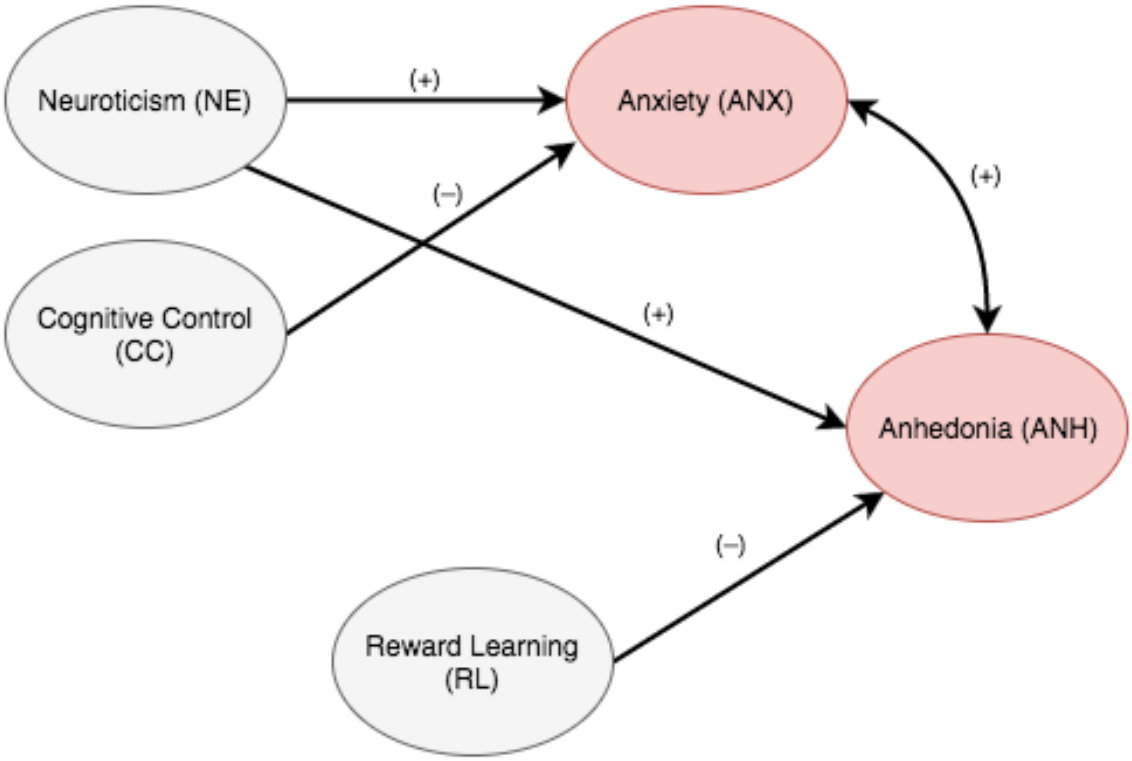

Figure 2. Hypothesized trimmed model without the interaction term NE×CC. Exogenous variables are shaded grey and endogenous variables are shaded red. The (+) or (–) signs indicate the hypothesized direction of the path coefficient; each are hypothesized to reach significance at $p < .05$. The curved double-headed arrow indicates correlated disturbances.

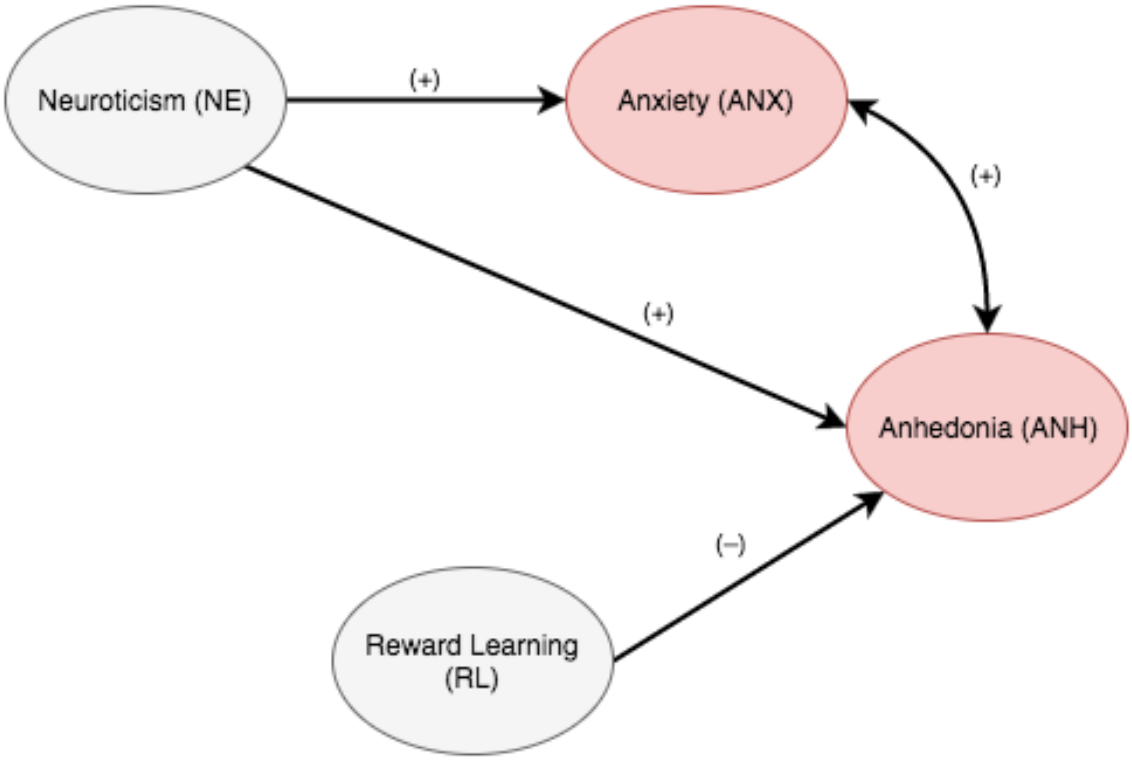

Figure 3. Hypothesized trimmed model without NE×CC and CC terms. Exogenous variables are shaded grey and endogenous variables are shaded red. The (+) or (–) signs indicate the hypothesized direction of the path coefficient; each are hypothesized to reach significance at $p <$ .05. The curved double-headed arrow indicates correlated disturbances.

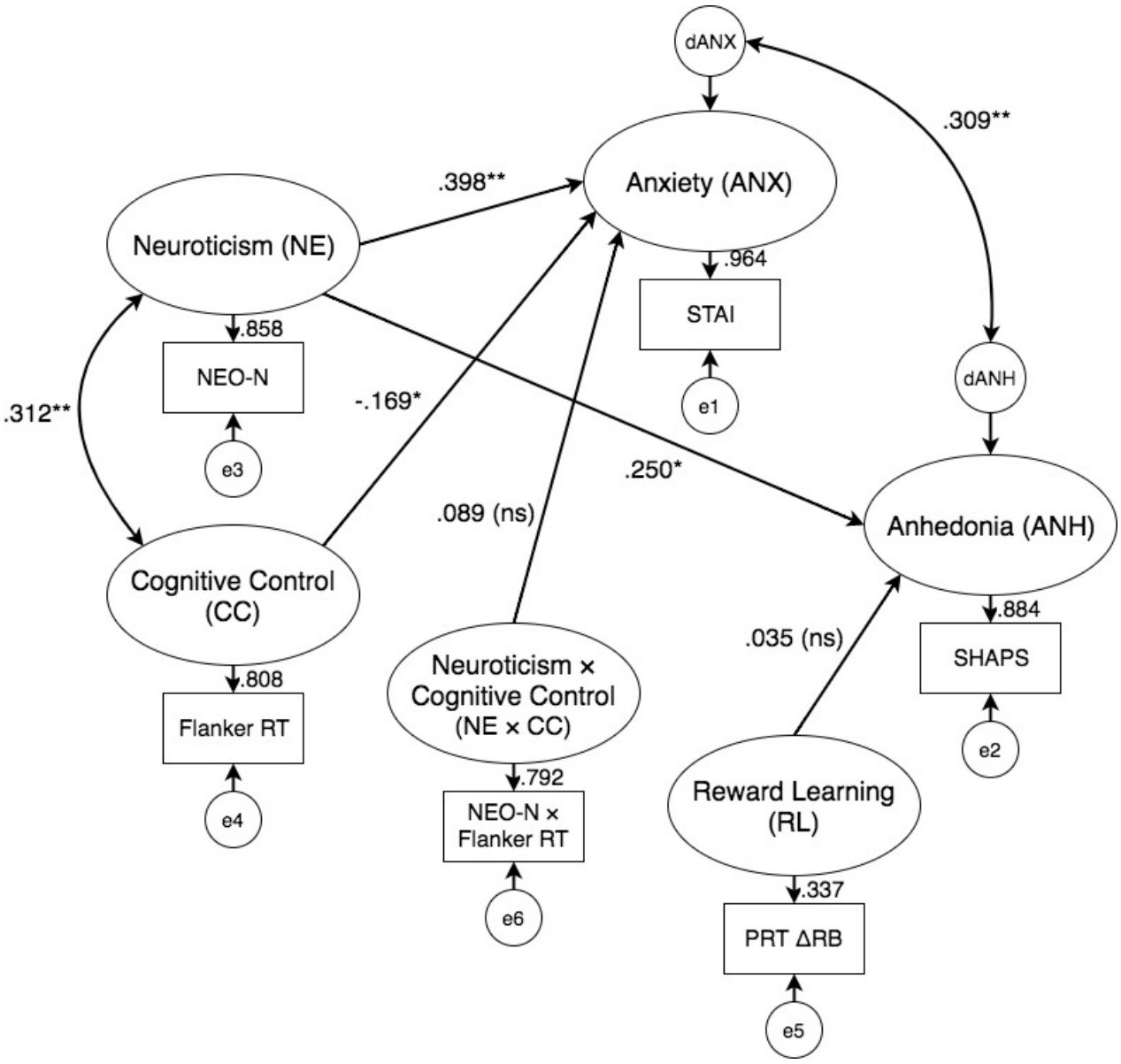

Figure 4. Model 1: Estimated full model. Rectangles represent observed variables, and ovals represent latent variables. Circles represent errors and disturbances. Single headed arrows represent standardized direct effects. The curved double-headed arrows indicate correlations. Nonsignificant correlations between exogenous variables are not shown. *$p < .05$; **$p < .001$; (ns) indicates nonsignificant effect.

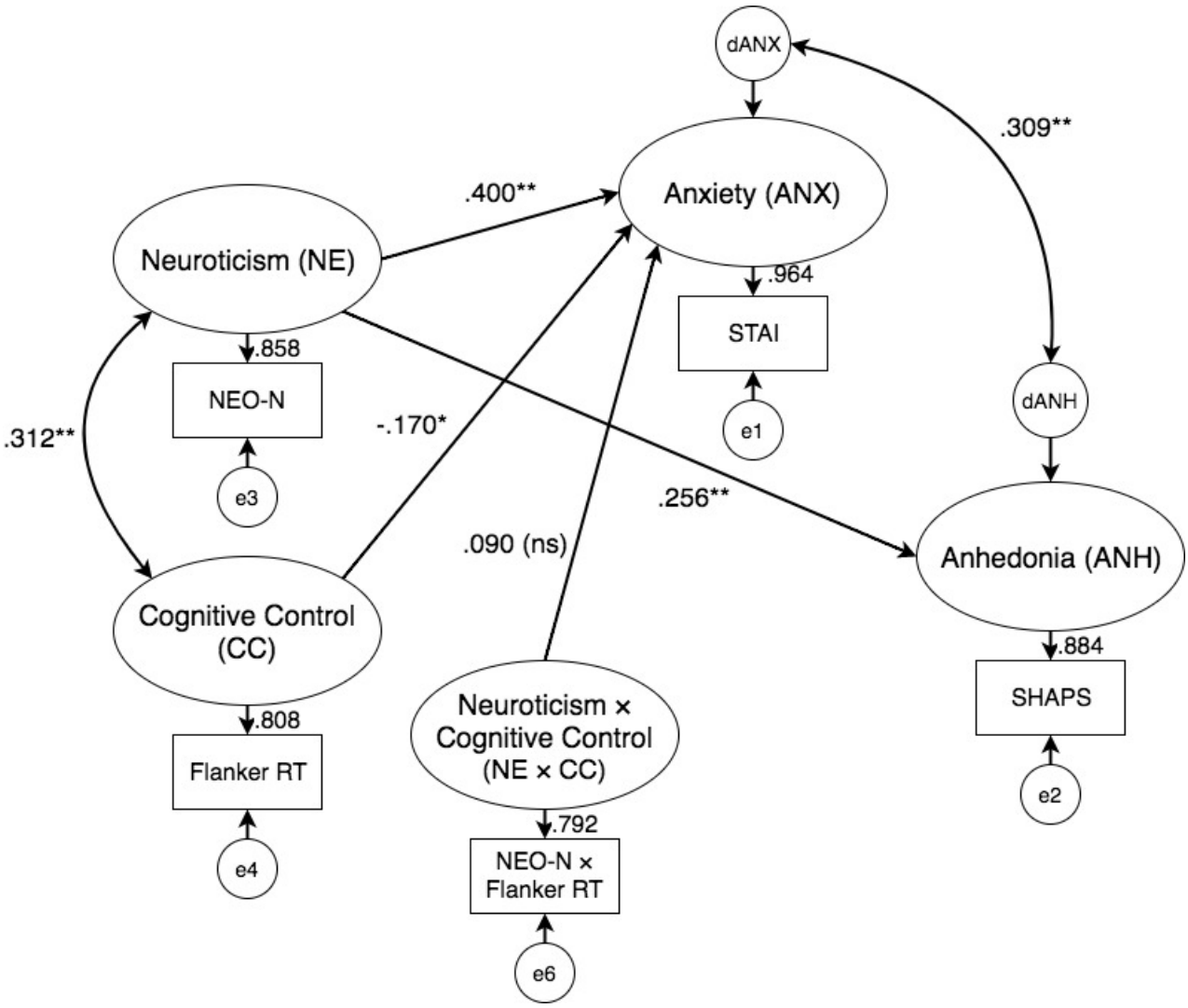

Figure 5. Model 2: Trimmed model without the RL term. Rectangles represent observed variables, and ovals represent latent variables. Circles represent errors and disturbances. Single headed arrows represent standardized direct effects. The curved double-headed arrows indicate correlations. Nonsignificant correlations between exogenous variables are not shown. *$p < .05$; **$p < .001$; (ns) indicates nonsignificant effect.

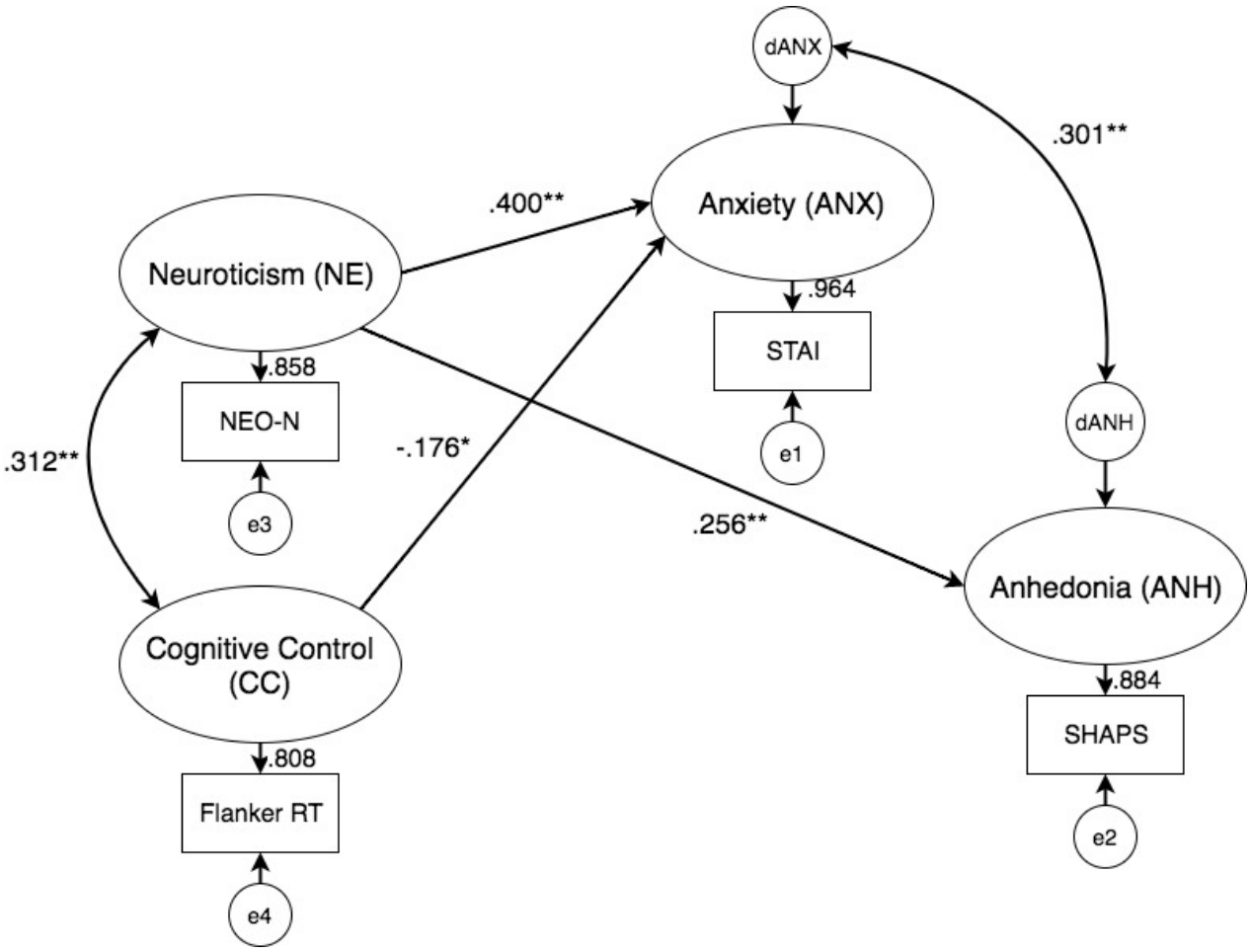

Figure 6. Model 3: Final model without the RL term and NE×CC terms. Rectangles represent observed variables, and ovals represent latent variables. Circles represent errors and disturbances. Single headed arrows represent standardized direct effects. The curved double-headed arrows indicate correlations. Nonsignificant correlations between exogenous variables are not shown. *$p < .05$; **$p < .001$

APPENDICES

Appendix A. Self-Report Measures

Snaith-Hamilton Pleasure Scale (P)

This questionnaire is designed to measure your ability to experience pleasure in the last few days. It is important to read each statement very carefully. Select the answer that corresponds to how much you agree or disagree with each statement.				
I would enjoy my favorite television or radio program.	○ Strongly Disagree	○ Disagree	○ Agree	○ Strongly Agree
I would enjoy being with my family or close friends.	○ Strongly Agree	○ Agree	○ Disagree	○ Strongly Disagree
I would find pleasure in my hobbies and past-times.	○ Strongly Disagree	○ Disagree	○ Agree	○ Strongly Agree
I would be able to enjoy my favorite meal.	○ Strongly Agree	○ Agree	○ Disagree	○ Strongly Disagree
I would enjoy a warm bath or refreshing shower.	○ Strongly Agree	○ Agree	○ Disagree	○ Strongly Disagree
I would find pleasure in the scent of flowers or the smell of a fresh sea breeze or freshly baked bread.	○ Strongly Disagree	○ Disagree	○ Agree	○ Strongly Agree
I would enjoy seeing other people's smiling faces.	○ Strongly Agree	○ Agree	○ Disagree	○ Strongly Disagree
I would enjoy looking smart when I have made an effort with my appearance.	○ Strongly Disagree	○ Disagree	○ Agree	○ Strongly Agree
I would enjoy reading a book, magazine or newspaper.	○ Strongly Agree	○ Agree	○ Disagree	○ Strongly Disagree
I would enjoy a cup of tea or coffee or my favorite drink.	○ Strongly Disagree	○ Disagree	○ Agree	○ Strongly Agree
I would find pleasure in small things, e.g. bright sunny day, a telephone call from a friend.	○ Strongly Disagree	○ Disagree	○ Agree	○ Strongly Agree
I would be able to enjoy a beautiful landscape or view.	○ Strongly Agree	○ Agree	○ Disagree	○ Strongly Disagree
I would get pleasure from helping others.	○ Strongly Disagree	○ Disagree	○ Agree	○ Strongly Agree
I would feel pleasure when I receive praise from other people.	○ Strongly Agree	○ Agree	○ Disagree	○ Strongly Disagree

Note: Due to copyright laws, the State-Trait Anxiety Inventory (STAI) and the NEO-FFI-3 (NEO-Five Factor Inventory-3) are not reproduced here.

Appendix B. Quality Control Procedures for Behavioral Tasks

Quality control checks for the Flanker Task and Probabilistic Reward Task (PRT) were used to flag cases with datasets characterized by unusual outlier performance, which may be due to factors such as misunderstanding of task instructions, lack of participation in the task, or other interfering factors associated with the testing environment or administration. In such cases, the scores produced were unlikely to be accurate representations of the constructs that the behavioral tasks are intended to measure. This analysis was conducted as part of data processing by the EMBARC study team (Webb et al., 2016) prior to release of data to this author. Outlier trials were defined as those in which the raw RT was less than 150 ms or the log-transformed RT exceeded the participant's mean±3SD, computed separately for congruent and incongruent stimuli in the Flanker Task. In the Flanker Task, datasets that did not meet quality control standards had: ≥ 35 outliers (i.e., > 10% of trials), < 200 outlier-free congruent trials, < 90 outlier-free incongruent trials, or < 50% correct for congruent or incongruent trials. In the PRT, datasets that did not meet quality control standards had: (1) > 80 outliers in each block (i.e., > 10% of trials), (2) ≥ 24 rich rewards or ≥ 7 lean rewards in each block, (3) rich-to-lean reward ratio ≥ 2.5 in any block, and (4) rich or lean accuracy ≥ 0.40 in any block.

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