OPERATIONALIZING NEUROTICISM USING TASK-BASED FMRI AND PSYCHOLOGICAL MEASURES IN A LARGE SAMPLE

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Abstract

Background: Trait neuroticism is characterized by individual differences in the experience of, and proclivity toward, negative emotions. As such, neuroticism has been associated with increased rates of transdiagnostic psychopathology. The emerging field of personality neuroscience aims to explain the underlying neurobiological sources for individual personality variation. A limited number of studies, mostly in relatively small samples, have examined the relationship between individual differences in trait levels of neuroticism and patterns of brain activation, assessed using functional neuroimaging, typically during negative emotion processing tasks. In particular, studies have suggested an association between neuroticism and magnitude of amygdala activation, rate of amygdala habituation, and amygdala-prefrontal cortex connectivity. The results of these studies are, at times, contradictory and generally inconclusive.

Methods: In the current project, we examine the relationship between trait neuroticism and these three hypothesized neural markers (amygdala activation, amygdala habituation, and amygdala-prefrontal connectivity) during negative emotion processing in a large sample (N=663) of twins from the Minnesota Center for Twin and Family Research. Participants were scanned during a negative emotional face-matching task.

For Aim 1 of this project, twin pairs were broken up such that we examined each hypothesized marker in a group of first-born twins and replicated the analyses in a group of second-born twins, resulting in two large sub-samples. Using a series of general linear models (GLM) in FSL software, amygdala activation, amygdala habituation, and amygdala-prefrontal functional connectivity (assessed using a psychophysiological

interaction [PPI]) in response to negative face processing were analyzed and neuroticism scores were included as a regressor in the models.

For Aim 2, this study utilized a multivariate approach in the full sample by developing a psychoneurometric model in an effort to refine the construct of trait neuroticism. This method utilizes multiple indicators across different measurement domains (e.g., psychological domain, neuroscientifically-derived domain) in an attempt to better characterize the latent trait of neuroticism. Three self-report measures for neuroticism and three hypothesized neural measures of neuroticism (magnitude of amygdala activation, rate of amygdala habituation, and amygdala-prefontal cortex connectivity) were used in attempt to build a psychoneurometric model to better characterize trait neuroticism.

Results: Across both twin groups, neuroticism did not show a reliable association with magnitude of brain activation in the amygdala or with amygdala habituation during the negative emotional face matching. Across both twin groups, PPI analyses revealed that amygdala–vmPFC connectivity during emotional face matching was positively correlated with neuroticism scores. Results of the psychoneurometric model suggest that there is no reliable relationship among the three hypothesized neural markers or between the hypothesized neural markers and the self-report measures of neuroticism.

Conclusions: The corticolimbic circuitry involving the vmPFC and amygdala has been associated with emotion regulation and increased vmPFC activity has been correlated with reduced activation in the amygdala. The results of the current study suggest that the regulatory function of the vmPFC may be diminished in individuals who are higher in neuroticism or that emotion regulation may be more effortful in these individuals. Additionally, these findings, replicated across two large samples, suggest that magnitude

of amygdala activation and rate of amygdala habituation may not serve as useful neural correlates of neuroticism. There is evidence that habituation of other brain regions might be an area deserving further research. Taken together, these findings suggest that trait neuroticism may represent a failure in top-down control and regulation of emotional reactions, rather than from overactive, emotion perception processes. The current project highlights the challenges of employing fMRI in building a psychoneurometric model for personality domains and suggests future directions for such studies.

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Defining Trait Neuroticism

Trait neuroticism is a relatively stable personality domain reflecting individual differences in threat and punishment sensitivity as well as the tendency toward negative affect including emotions such as fear, anger, worry, frustration, sensitivity to criticism, hostility, vulnerability, self-consciousness and frustration (DeYoung, 2015; Widiger, 2009). Individuals high in neuroticism tend to interpret events as more threatening, react more negatively to events, and utilize maladaptive, avoidant and defensive coping strategies, such as anger, irritability, depression, panic, and anxiety, in the face of negative events (McCrae & Costa, 2003; Tackett & Lahey, 2016). This proneness to negative emotionality and maladaptive behavior predicts a multitude of adverse functional outcomes; neuroticism is inversely correlated with marital satisfaction, occupational success, and quality of life (Lahey, 2009). As a result, trait neuroticism has been associated with an enormous economic cost to society, a cost which exceeds that of common mental disorders (Cuijpers et al., 2010).

Neuroticism, historically, has been assessed and understood using descriptive taxonomic approaches, such as self- or other-report, to quantify variation in trait levels across people. Using such methods and cross-sectional study design, a substantial body of research over the last two decades has found neuroticism to be associated with a range of

psychopathology across the spectrum (internalizing, externalizing, and psychotic disorders (Barrantes-Vidal, Ros-Morente, & Kwapil, 2009; Bienvenu & Stein, 2003; Hopwood, Thomas, Markon, Wright, & Krueger, 2012; Krueger, 2005; Krueger & Tackett, 2003; Watson et al., 1994). Longitudinal study designs have also found neuroticism to be predictive of common mental disorders , though the association is weaker using prospective study designs (de Graaf, Bijl, Ravelli, Smit, & Vollebergh, 2002; Kendler, Neale, Kessler, Heath, & Eaves, 1993; Lahey, 2009; Ormel, Oldehinkel, & Vollebergh, 2004). Multiple models for the relationship between neuroticism and common mental disorders have been developed, though the exact etiology of the relationship remains uncertain (Ormel, Jeronimus, et al., 2013).

Still, because neuroticism has been shown to be both associated with and, in some studies, predictive of such a wide range of psychopathology, it has been suggested that trait neuroticism may represent a transdiagnostic, underlying liability factor. In this way, trait neuroticism may help to explain the correlations and comorbidity that exists across psychiatric disorders (Lahey et al., 2012). Taken further, this perspective implies that it might be possible to prevent or treat the negative corollaries of neuroticism and, in doing so, help reduce the likelihood of onset or severity of associated psychopathology (Barlow, Sauer-Zavala, Carl, Bullis, & Ellard, 2014; Conrod et al., 2000; Conrod et al., 2013; Conrod, Castellanos, & Mackie, 2008; Lahey, 2009). This view of neuroticism as a non-specific liability factor for mental disorders suggests that it might usefully fit into transdiagnostic, dimensional conceptualizations of psychopathology which have been gaining traction in recent years (Buckholtz & Meyer-Lindenberg, 2012; Robert F Krueger & Markon, 2011).

Different Theoretical Perspectives on Trait Neuroticism

Though the term neuroticism has longstanding roots in the Freudian tradition, the modern idea of neuroticism was introduced by Hans Eysenck in the late 1960's (Eysenck, 1967). Since then, the concept of neuroticism has emerged in personality psychology from numerous research traditions, using both lexical and psychophysiological methods (Ormel, Jeronimus, et al., 2013). In diverse trait and dispositional models of personality, a higher-order dimension or factor akin to neuroticism emerges. Sometimes referred to as negative affectivity or negative emotionality (Rothbart, Ahadi, Hershey, & Fisher, 2001; Shankman & Klein, 2003; Tellegen & Waller, 2008), evidence for a robust, neuroticism factor emerges across ages, cultures, and gender (Costa, Terracciano, & McCrae, 2001; Hofstede & McCrae, 2004; McCrae & Costa, 1997).

In the Five Factor Model of personality (FFM), which is the most widely accepted personality trait model, neuroticism is one of the higher order domains along with agreeableness, conscientiousness, openness, extraversion (Digman, 1990; Goldberg, 1993; McCrae & Costa, 2003). The FFM emerges from the lexical hypothesis, which argues that the personality characteristics which are most important to people will emerge in language and that more important characteristics will emerge more frequently in language. Derived using associated methods, neuroticism within the FFM typically refers to a dimension of maladjustment or negative emotionality vs. adjustment and emotional stability. From the psychophysiological literature, neuroticism (or negative emotionality) also developed as a core personality dimension, and it generally refers to individual differences in to the tendency toward emotional arousal and failures in emotion inhibition

(Eysenck & Eysenck, 1985). From this tradition, these differences in response styles were understood to stem from individual differences in the functioning of aspects of the central nervous system.

Variations in how neuroticism is conceptualized across trait models typically stem not only from the methods used to study it, but also from differences in the lower order facets or features that contribute to the higher order domains (Ormel, Bastiaansen, et al., 2013). For example, in three-factor trait models, there is no separate domain of agreeableness. As a result, negative emotionality includes aspects of antagonism, aggression, agentic negative emotionality, and alienation, also referred to as alienated negative emotionality (Patrick, Curtin, & Tellegen, 2002; Rothbart et al., 2001; Tackett & Lahey, 2016; Tellegen & Waller, 2008). Within neuroticism in the FFM, DeYoung and colleagues (2007) identify sub-aspects of neuroticism, withdrawal and volatility, which represent intermediaries between the higher order domain of neuroticism and the specific facets which comprise neuroticism. Despite these and other meaningful differences in the conceptualization of neuroticism across models of personality, the fundamental construct of neuroticism largely persists, and can be integrated across a range of models of both normal and abnormal personality in a consistent, hierarchical structure (Costa & McCrae, 1995; Markon, Krueger, & Watson, 2005).

Across conceptualizations, research has found evidence for consistent differences between genders in the mean level of neuroticism. Studies show that women have higher rates of neuroticism, as well as higher levels of related constructs, such as anxiety and low self-esteem (Costa et al., 2001; Feingold, 1994; Kling, Hyde, Showers, & Buswell, 1999). When controlling for the aspects of neuroticism, volatility and withdrawal, the

gender difference remained for withdrawal but not for volatility (Weisberg, De Young, & Hirsh, 2011). Psychiatric disorders most closely associated with neuroticism, such as depression and anxiety disorders, also present at higher rates in women relative to men (Weissman et al., 1996). These differences are most prominent during reproductive years, but are present throughout the lifespan (Jorm, 1987).

Part of what ties together many of the various trait models of personality is the basic motivation to uncover how personality traits and dispositions relate to both psychological processes and biological systems (DeYoung et al., 2010; Ormel, Bastiaansen, et al., 2013; Patrick et al., 2002). While self-report has been the predominant method of measuring neuroticism, relating personality to underlying biological processes has proven challenging and alluring. Substantial evidence supports the heritability of personality traits, such as neuroticism (Lahey, 2009; Van Den Berg et al., 2014; Widiger, 2009) further suggesting the likely existence of underlying biological processes which may explain individual differences in trait neuroticism. Advancements in research methodologies and technologies have moved such questions from the realm of the theoretical to the applied. The following section reviews the current research on the neurobiological correlates of neuroticism.

Biological Basis of Neuroticism

The past decade has seen the growth of the field of personality neuroscience, an area of research which emphasizes the need to tie personality dimensions to their relevant biological systems and which seeks to empirically test the idea that personality represents

biologically based individual differences (Adelstein et al., 2011; DeYoung, 2010). As human behavior and cognition emerges primarily from the brain, the processes associated with individual differences in personality are understood to emerge from differences in brain structure and function across individuals (Allen & Deyoung, 2016). This area of research aims to understand personality traits in the context of underlying neural systems, which can offer explanations for the cognitive, social, and affective correlates that are relevant to the dimensions of personality. Because of the clinical relevance of neuroticism, it has been the focus of more neuroscientific research, relative to the other FFM personality domains. One goal behind this push for increased research on the neural associations of neuroticism is to improve our understanding of the underlying biology behind the etiology, course, and potential treatments of psychiatric disorders across the spectrum of psychopathology (Ormel, Bastiaansen, et al., 2013).

Early studies into the biological underpinnings of trait neuroticism were largely based on studies of Eysenck's arousal theory of personality and Gray's reinforcement sensitivity theory of personality. Both of these theories suggest that neuroticism stems from the hyperarousal of certain key brain systems (e.g., limbic structures) with downstream effects on autonomic arousal and the hypothalamic-pituitary-adrenal (HPA) axis. This system is responsible for regulating the body's stress reaction in response to threats or danger. In Eysenck's theory, high neuroticism was hypothesized to be associated with lower activation thresholds and higher activation levels in regions of the limbic system (including the amygdala, hypothalamus, and hippocampus), with a particular focus on increased sensitivity of the amygdala (Eysenck, 1967). Gray proposed that trait anxiety (which, as he describes it, is largely overlapping with the definition of

neuroticism used in the current project) resulted from an interaction between the behavioral inhibition system and the flight-fight-freeze system, both of which are responsible for avoidance in response to threats and conflicts between goals (Gray, 1982, 1991; Gray & McNaughton, 2000). Gray (1990) theorized that both of these avoidance processes were driven by the brainstem, hypothalamus, and the amygdala. Early biological studies on these theories primarily utilized electrophysiological methods, such as skin conductance and salivary and urinal cortisol, which served as global measures of central nervous system arousability. This early theoretical work laid the groundwork for much of the research on the neural correlates of neuroticism that followed.

To better understand the relationship between theories of neuroticism and the brain, it is important to understand the structural and functional role that the amygdala plays. The amygdala, an almond shaped mass of gray matter, can be found in the medial temporal lobe of the brain, and is the brain region most closely associated with fear processing (Aggleton, 1992). A wealth of research from animal literature has provided the basis for understanding the association between the amygdala and its projections to other brain areas in response to threatening stimuli (Davis, 1992). In one of these pathways, the amygdala connects to downstream brain regions involved in coordinating behavioral, neuroendocrine, and autonomic responses to emotional stimuli, including the hypothalamus and the brain stem (Depue, 2009; Heimer, 2003; LeDoux, 1998; Ormel, Bastiaansen, et al., 2013). The amygdala also has connections to higher cortical brain regions including the anterior cingulate cortex (ACC) and regions in the prefrontal cortex (PFC), involved in self-referential processing and the cognitive control of emotions (Kim et al., 2011; Ochsner & Gross, 2005). These dual pathways of amygdala connectivity

have motivated research on the physiological and neural correlates of neuroticism. Though much of the early research examined the relationship between neuroticism and the neuroendocrine and autonomic responses, many of which are understood to be downstream effects of the amygdala, improved neuroimaging technologies have allowed researchers to better examine the structure and function of the amygdala as well as its connections with higher cortical brain regions.

Structural Neuroimaging and Neuroticism

Structural neuroimaging studies have examined associations between neuroticism and related psychological constructs (such as behavioral inhibition and harm avoidance) and a variety of structural measures including volume, thickness, and surface area in brain regions of interest. Studies have examined the association between amygdala volume and neuroticism, with several studies finding a positive association between amygdala volume and neuroticism (Barrós-Loscertales et al., 2006; Iidaka et al., 2006; Koelsch, Skouras, & Jentschke, 2013), while other studies have failed to find this association (Cherbuin et al., 2008; DeYoung et al., 2010; Fuentes et al., 2012; Liu et al., 2013). In a sample of over 1000 people, Holmes and colleagues found a weak but positive correlation (r=.10) between neuroticism and amygdala volume as well as a weak but positive correlation (also, r=.10) with the hippocampus (Holmes et al., 2012). This finding, in such a large sample, suggests that there is likely an association between amygdala size and neuroticism, but that the effect size is probably small. The small effect

size may help explain the inconsistency in the findings, as many smaller studies may have failed to reproduce this effect (Allen & Deyoung, 2016).

Additionally, studies have found a negative association between neuroticism and volume in prefrontal regions, such as the orbitofrontal cortex (OFC) and medial PFC (DeYoung et al., 2010; Fuentes et al., 2012). Other studies found negative associations between neuroticism and cortical thickness in the ACC and the medial PFC (Bjørnebekk et al., 2013; Holmes et al., 2012). The OFC and the medial PFC have been shown to play an important role in self-evaluation and downstream suppression of negative emotion through an inhibitory relationship with the amygdala (Davidson & Irwin, 1999; Heatherton, Macrae, & Kelley, 2004; Ochsner & Gross, 2005). Both poor self-esteem and emotion dysregulation are characteristic of individuals high in neuroticism, underscoring the potentially important role of this region in the higher-order processes associated with neuroticism.

In addition to structural MRI, diffusion tensor imaging (DTI) enhances our understanding of differences in brain structure by providing information about the microstructure and integrity of the brain's white matter tracts. In this way, DTI serves as a useful metric by which to measure individual differences or between-group differences in neural structural connectivity. Studies have found that increased neuroticism and related constructs are associated with reduced white matter integrity in certain corticolimbic tracts involved in the emotion processing neurocircuitry (Taddei, Tettamanti, Zanoni, Cappa, & Battaglia, 2012; Westlye, Bjørnebekk, Grydeland, Fjell, & Walhovd, 2011; Xu & Potenza, 2012) but also in disparate anatomical regions spread throughout the brain (Bjørnebekk et al., 2013). These findings suggest that the neuronal

synchronization and integration of regions important for emotion regulation circuitry may be impaired, but these findings also suggest that neuroticism may be associated with widespread alterations in brain connectivity. This is consistent with research on anxiety disorders, which showed altered structural connectivity associated with anxiety disorders in tracts throughout the brain (Ayling, Aghajani, Fouche, & van der Wee, 2012).

Neural Activation and Neuroticism

A growing body of research has employed fMRI to identify neural correlates of trait neuroticism, particularly during negative emotion processing (Ormel, Bastiaansen, et al., 2013; Servaas et al., 2013). fMRI studies of negative emotion processing have been useful for identifying individual differences in brain activation associated with emotion processing and threat sensitivity, a theoretical functional neural correlate for trait neuroticism. Basic emotion research has provided evidence for the important role of the amygdala functions in emotional learning and memory, negative emotion processing, and appraising threat (Britton, Lissek, Grillon, Norcross, & Pine, 2011; Davis & Whalen, 2001; Morris et al., 1998). Given its association with emotion and face processing, it has been suggested that activation in the amygdala might directly relate to individual differences in trait neuroticism (Canli, 2008).

A number of studies have found evidence for this theory, with findings showing a positive correlation between amygdala activation and trait neuroticism, using diverse paradigms involving affective content, such as emotional scenes and faces, the emotional Stroop task, and an emotional prosody task (Brück, Kreifelts, Kaza, Lotze, & Wildgruber,

2011; Chan, Norbury, Goodwin, & Harmer, 2009; Cunningham, Arbuckle, Jahn, Mowrer, & Abduljalil, 2011; Haas, Omura, Constable, & Canli, 2007; Harenski, Kim, & Hamann, 2009). Other studies examining the association between amygdala activation and neuroticism, though, using similar fMRI paradigms have failed to replicate this finding (Cremers et al., 2010; Drabant, McRae, Manuck, Hariri, & Gross, 2009; Haas, Constable, & Canli, 2008; Hyde, Gorka, Manuck, & Hariri, 2011; Thomas et al., 2011). Most of these studies have been conducted in relatively small samples, calling into question the results of the individual studies and helping to explain the inconsistencies in the findings (Yarkoni, 2009). A recent quantitative meta-analysis of fMRI and PET studies investigating neural activity associated with neuroticism, using parametric coordinate-based meta-analysis, also failed to find a positive association between amygdala activation and neuroticism across studies (Servaas et al., 2013). Unfortunately, the results of a meta-analysis based on primarily under-powered studies are difficult to interpret as well, leaving open the question about the relationship between amygdala activation and neuroticism (Allen & Deyoung, 2016).

One possible explanation for the differences seen across these studies is the possibility that gender might moderate patterns of brain activation associated with negative emotion processing. Previous studies have found evidence for different patterns of emotion processing in males and females, with men showing greater amygdala activation relative to females while processing happy emotions and different patterns of activation between the genders in response to negative emotions (Lee et al., 2002; Wrase et al., 2003). Differences in patterns of brain activation exist across genders, even when the emotional content is subliminal (Victor, Drevets, Misaki, Bodurka, & Savitz, 2017).

Furthermore, one study found neural differences between genders during emotion regulation processes, such as during cognitive reappraisal (McRae, Ochsner, Mauss, Gabrieli, & Gross, 2008). In this study, despite similar behavior across genders in response to emotion content, fMRI data revealed reduced prefrontal activation and decreased amygdala activation in males during emotion regulation, relative to females. The authors suggest that these findings might indicate a more automatic, less effortful emotion regulation process in males relative to females. Such findings underscore the importance of examining gender differences in brain activation, particularly in connection with neuroticism, a personality trait which has shown consistent differences across gender (Costa et al., 2001; Weisberg et al., 2011).

In addition to the amygdala, fMRI studies have found associations between neuroticism and activation in prefrontal regions, such as the ACC and medial PFC, brain regions associated with emotion regulation and self-evaluation. During sustained processing of negative information, Haas and colleagues (2008) found neuroticism to be associated with ongoing activation in the medial PFC while responding to sad emotional faces, but not fearful or happy faces. In addition to finding an association between activity in the medial PFC and neuroticism, this study also found evidence for a meaningful relationship between the temporal dynamics of brain activation in the medial PFC and trait neuroticism. Another study found that increasing emotional well-being (and reduced neuroticism) associated with aging, might be tied to greater medial PFC activation while processing fearful emotional faces and reduced medial PFC activation while processing happy faces (Williams et al., 2006). During a study of self-referential processing and negative emotionality, researchers found an association between increased

activation in the dorsal medial PFC and the posterior cingulate cortex, particularly while viewing negative pictures and judging whether they were related to the self or not (Lemogne et al., 2011). These findings suggest an alternative neural theory to explain trait neuroticism – namely, that individual differences in neuroticism may be related to regions associated with top-down control of negative emotionality, rather than with regions associated with emotion generation (such as the amygdala).

Neural Habituation and Neuroticism

As was suggested above, some recent research has shifted focus from examining the magnitude of brain activation in regions of interest, such as the medial PFC or the amygdala, to the temporal dynamics of activation in these brain regions as a possible neural marker of neuroticism. Schuyler and colleagues (2014), in a relatively large sample of 120 individuals, found that while initial amygdala activation magnitude after seeing negative images was not predictive of trait neuroticism, a slower recovery time for the amygdala to return to baseline was predictive of neuroticism. Time to recovery, or habituation, has been defined as differential response amplitude to repeated stimuli over time. Neural habituation enables an individual to ignore known information and to, instead, focus on novel information. Failure to habituate though indicates that the individual may have difficulty learning that an environment is familiar or predictable. Likely, a longer time course for the amygdala may indicate difficulty recovering from emotionally evocative stimuli, which is in line with the phenotypic presentation of trait neuroticism.

Though historically studies have examined differences in magnitude, averaged across a task, there is reason to believe that habituation may be a sensitive individual difference marker. One study found that differences in magnitude between the left and right amygdala activation could actually be explained by differences in habituation rates (Phillips et al., 2001). Differences in habituation may, partially, explain genetic differences seen in individuals with certain polymorphisms (5-HTTLPR and not COMT genotype groups) associated with amygdala reactivity (Lonsdorf et al., 2011). One recent study found that amygdala habituation (during negative emotion processing) was a more reliable neural marker, exhibiting higher within-subject reliability in test-retest, than magnitude of amygdala activation. This finding suggests that amygdala habituation might be more amenable to individual difference research, and might be useful for a study like the current project, examining individual differences in a dimensional personality trait (Plichta et al., 2014).

Psychopathology research lends credence to the idea that altered patterns of neural habituation in response to negative stimuli might be an important neural correlate of various psychiatric disorders. A recent study found that higher social fearfulness was associated with reduced habituation in regions of the social brain, including the hippocampus, amygdala, vmPFC, medial orbitofrontal cortex, fusiform face area and visual cortex (Avery & Blackford, 2016). Another study found that rapid habituation of the ventral striatum was associated with post-partum depression (Moses-kolko et al., 2011). A study examining neural habituation in a sample of individuals with borderline personality disorder (BPD) found that, relative to healthy controls, individuals with BPD did not show any increase in activation of the dorsal anterior cingulate cortex over the

course of a task involving viewing negative stimuli, whereas in healthy controls activity in this region increased over repeated viewings of the negative stimuli (Koeningsberg et al., 2014). These various studies underscore the importance of examining the associations between the time course of neural activation in regions of interest and psychological and psychopathological constructs of interest.

Neural Connectivity and Neuroticism

As reviewed above, findings from task-based fMRI often reveal distributed patterns of altered brain activation associated with trait neuroticism and in studies of psychiatric patients relative to healthy controls. Such findings highlight the fact that multiple brain regions are often involved in cognitive and affective processes. As such, interactions between brain regions during task-based fMRI may be informative and reliable patterns of neural activity associated with psychopathology (Buckholtz & Meyer-Lindenberg, 2012; Friston, 2005; Sporns, 2011). Network connectivity models, instead of studying the specialized processing occurring in specific brain regions, examine the contemporaneous flow of information across distributed brain systems (Mesulam, 1998). Evidence using both structural and functional data suggests that there may be specific patterns of dysconnectivity between limbic and prefrontal regions which characterize trait neuroticism and which may be a useful neural correlate for examining individual differences in neuroticism (Bjørnebekk et al., 2013; Cremers et al., 2010; Servaas et al., 2015; Servaas et al., 2013; Xu & Potenza, 2012).

Using connectivity analyses (psychophysiological interactions [PPI]) during an event related negative emotion processing task, Cremers and colleagues (2010) found that amygdala-ACC connectivity was inversely correlated with trait neuroticism in a community sample of 60 individuals. Another study, examining trait anxiety, found a similar association between amygdala-ACC dysconnectivity in a sample of 13 men (Kienast et al., 2008). Given the important role that these prefrontal brain regions play in cognitive control of emotions, reduced connectivity between the amygdala and areas of the prefrontal cortex could provide a neural basis for negative emotion sensitivity associated with neuroticism (Ochsner & Gross, 2005). Such findings suggest that dysconnectivity between brain regions involved in emotion generation and brain regions involved in emotion regulation might underlie the experience of negative emotions characterized by neuroticism. These functional dysconnectivity models are supported by structural connectivity studies, typically measured using DTI and reviewed above, which suggest a similar pattern of structural connectivity associated with neuroticism (Xu & Potenza, 2012).

Even in the absence of a task, while the brain is at rest, there is evidence that connectivity and co-activation of brain regions may be associated with personality traits, such as neuroticism. Adelstein and colleagues (2011) used a seed-based approach to analyze resting state data and found increased resting state functional connectivity within the precuneus and between the precuneus and the dorsal-medial PFC, indicating higher connectivity between limbic and cognitive brain regions and suggesting increased integration of information about social and emotional contexts. Another study found neuroticism to be negatively associated with activity in the middle frontal gyrus and

precuneus, measured using spontaneous low-frequency oscillations from resting-state fMRI (Kunisato et al., 2011). One potential benefit to using resting state analyses for personality neuroscience is that resting state functional connectivity is generally stable over time, making patterns of resting state connectivity potentially similar to stable personality traits.

Psychoneurometric Model

While a large body of literature has been dedicated to understanding the psychological properties and psychopathological correlates of neuroticism, and to a lesser extent the neural correlates of neuroticism, including the patterns of task-related neural activation associated with neuroticism, these literatures exist largely separate from one another. Bridging these areas of research, using a multivariate-psychobiological approach, could not only elucidate the relationship between psychological and neural indicators but could also help to refine the latent construct of neuroticism. Such a hetero-phenomenological approach has been conceptualized as 'psychoneurometrics,' which encourages the study of transdiagnostic constructs, such as neuroticism, using indicators from multiple domains of measurement (Patrick et al., 2013; Yancey, Venables, & Patrick, 2015).

Because trait personality psychology is relevant to psychopathology and is, by definition, focused on dimensional individual differences, it can be a useful model for bridging the categorical phenomena found in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the dimensional approach to researching mental disorders

advocated by the National Institute of Mental Health (NIMH) through the Research Domain Criteria (RDoC) (Insel et al., 2010). RDoC is a funding framework for research on the biology of psychiatric disorders, which encourages a dimensional approach to research on psychopathology that cuts across multiple levels of analysis (from genes and molecules all the way up to behavior and self-report). Though not entirely overlapping constructs, neuroticism usefully relates to the RDoC construct of negative valence (David Watson, Stanton, & Clark, 2017). Focusing on broader, transdiagnostic constructs such as neuroticism will enable researchers to draw from the large body of personality psychology research in the service of psychopathology research. Additionally, studying dimensional constructs such as neuroticism could help to move the field away from problematic categorical diagnoses and more in line with evidence-based mental illness research (Krueger & Eaton, 2010).

The psychoneurometric approach is a multivariate method for simultaneously modeling neurobiological indicators (e.g., diverse patterns of brain activation during a task believed to relate to the construct of interest) and psychological indicators (e.g., responses on self-report measures) to better articulate individual differences in constructs which are relevant to psychopathology, such as neuroticism. Such an approach incorporates neurobiological approaches into the conceptualization of psychological constructs, across multiple domains of measurement, making this approach directly compatible with the goals of RDoC (Macnamara & Luan Phan, 2016) . Recent studies have used this approach to characterize latent traits, such as threat sensitivity and dispositional liability for suicidal behavior, combining self-report measures and

neurophysiological indicators to better articulate these transdiagnostic constructs of clinical importance (Venables et al., 2017; Yancey et al., 2015).

As the word psychoneurometrics suggests, psychoneurometric modeling involves the combination of psychometric and neurometric information into a single model, in an effort to better estimate a latent variable (Patrick et al., 2013). In the current project, a psychometric latent variable of neuroticism is estimated using three self-report variables measuring neuroticism. Additionally, a neurometric latent variable neuroticism is estimated using three functional MRI variables hypothesized to all be related to trait neuroticism. Both latent variables are hypothesized to be an estimation of the continuous construct of neuroticism that exists in nature, but neither are a true measure of this trait. The psychoneurometric latent variable of neuroticism is estimated simultaneously by the self-report measures from the psychometric model and the brain measures from the neurometric model. By using two different types of indicators, the latent trait estimated is a better approximation of the "neuroticism" that truly exists in nature. In order to validate the utility of a psychoneurometric model of neuroticism, it should be able to predict associated negative outcomes, such as DSM-5 diagnoses of depression or anxiety disorders or poorer quality of life, associated with neuroticism, than a purely psychometric or purely neurometric neuroticism. A visual depiction of the psychoneurometric process is presented in Figure 6a.

A goal of the current project is to utilize a psychoneurometric approach by simultaneously modeling the various psychological indicators (self-report measures) and neural indicators (from task-based brain activation measured during fMRI) to better articulate the latent construct of neuroticism. Better integrating neuroscience research

with personality literature will enhance the field of personality psychology, which would benefit from novel methods with which to conduct multitrait, multimethod research on construct validity (Campbell & Fiske, 1959; Roberts et al., 2006). Additionally, this method would serve to validate the use of the hypothesized neural markers from the emotional-face matching task for measuring neuroticism. The hope is that this project not only serve to refine the construct of trait neuroticism, but that it will also validate the relatively novel psychoneurometric methodology, which may have broad appeal given its relevance to the RDoC framework.

Current Study Aims:

Aim 1a. Estimate the bivariate relationships between trait neuroticism and neural indicators of emotion reactivity. I hypothesize that (a) trait neuroticism will be positively correlated with magnitude of amygdala activation during negative emotion processing. Second, I hypothesize that (b) there will be an association between trait neuroticism and amygdala-vmPFC coupling during negative emotion processing. Last, I hypothesize that (c) trait neuroticism will be positively correlated with attenuated amygdala habituation over the course of the task.

Aim 1b. Estimate the bivariate relationships between trait neuroticism and neural indicators of cognitive control of emotions. I hypothesize that (a) trait neuroticism will be correlated with magnitude of vmPFC activation during negative emotion processing. Second, I hypothesize that (b) trait neuroticism will be positively correlated with attenuated vmPFC habituation over the course of the task.

Aim 1c. Test whether findings from Aim 1a and 1b are associated with unique aspects of neuroticism, withdrawal and volatility. I hypothesize that (a) it will be possible to identify unique aspects of trait neuroticism, by approximating withdrawal and volatility factors from the measures used in the current dataset. Using these unique factors, I hypothesize (b) that these distinct aspects of neuroticism will have different associations with the neural markers of neuroticism.

Aim 1d. Test whether findings from 1a and 1b vary across genders. I hypothesize that (a) there will be differences in the relationship between the hypothesized patterns of neural activation and trait neuroticism in males and females.

Aim 2. Estimate latent trait neuroticism by simultaneously modeling the two measurement domains: psychological (using self-report measures) and neural (hypothesized neural indicators). The goal is to better understand how these indicators relate to each other and to a latent factor of neuroticism. I hypothesize that (a) construct validity of the latent neuroticism factor will be improved using both neural and psychological indicators. Second, I hypothesize that (b) a hierarchical bifactor model will best capture the data, in which there is a higher order factor for the latent construct of neuroticism and lower order factors of psychologically derived neuroticism and neurally derived neuroticism.

Methods:

Participants:

The current study consisted of 663 same-sex male and female twin pairs and individuals (See Figure 1, Consort Diagram) from an older male-female (MF) cohort and a younger enrichment sample (ES) cohort of the Minnesota Twin and Family Study (MTFS; Iacono, Carlson, Taylor, Elkins, & McGue, 1999). The data from the current study was drawn from ongoing data collection in November 2016. In the data, there are 272 complete twin pairs and 119 individuals (from a twin pair). Data from the current study was collected at the 4th follow-up visit for the ES cohort and the 6th follow-up visit for the MF cohort. The average age across the sample in the current study is 30.40 (range = 23.36- 37.48; sd = 5.19) and the average age of the older (MF) cohort is 34.79 (range = 33.01-37.48; sd = 1.18) and for the younger (ES) cohort is 24.49 (range= 23.36-26.27; sd = .66). The sample is 54.00% female. The task and measures described in the current study were selected from a larger battery of assessments administered during a day-long laboratory visit as part of a larger study. The study was approved by the University of Minnesota's Institutional Review Board and all participants were given monetary compensation for their participation in the day long assessment as well as a separate compensation for completing the MRI portion of the assessment. After a variety of exclusion criteria were applied, which will be enumerated below, the final sample of participants was 548 individuals. There were no differences between participants in age or sex (p-values greater than .4).

Personality Questionnaires:

Participants completed three self-report measures, all known to assess aspects of trait neuroticism: a shortened version of the *Inventory for Depression and Anxiety Symptoms*-II (IDAS-II; Watson et al., 2012), the *Personality Booklet, Youth Abbreviated* (PBYA; Tellegen & Waller, 2008), which is a shortened version of the *Minnesota Personality Questionnaire* (MPQ), and the *Personality Inventory for DSM-5* (PID-5; Krueger, Derringer, Markon, Watson, & Skodol, 2012).

Inventory for Anxiety and Depression Symptoms-II: The IDAS-II is a 64-item questionnaire with a 5-point response scale (1, *Not at all* to 5, *Extremely*). While the full IDAS-II has 18-scales assessing symptoms of anxiety, depression, and mania from the past two weeks, in the current study, a shortened version of the IDAS-II was used with 38-items assessing scales of Dysphoria, Panic, Suicidality, Social anxiety, and Traumatic avoidance and Traumatic intrusions associated with PTSD. In the current project, Dysphoria was used to derive a neuroticism factor (Simms, Grös, Watson, & O'Hara, 2008).

Though the IDAS-II was developed as an assessment for DSM-IV depression and anxiety symptoms, the Dysphoria scale reflects a broader general factor associated with general distress and negative affect and correlates highly with Big Five measures of neuroticism and negative affect (David Watson, Gamez, & Simms, 2005; Watson & Naragon-Gainey, 2014). As such, along with other measures, the Dysphoria factor from the IDAS-II provides self-report information about general aspects of negative affect associated with mood and anxiety disorders. Watson et al. (2012) provides psychometric details in large university and community samples. Chronbach's alphas for the 6 primary

scales in the current sample range from .83–.92, suggesting that the internal consistencies are good and the majority of variance of any scale is shared.

Personality Booklet—Youth Abbreviated (PBYA): The PBYA, which was constructed specifically for the Minnesota Twin and Family Study, is a 138-item questionnaire with a 4-point response scale (1, *Definitely true*, to 4, *Definitely false*) and was originally developed for participants younger than 16, though it has been used in older samples as well. Both the items and the scale composition are identical between the PBYA and MPQ, but the PBYA has fewer scales. Developed through iterative factor analysis, the MPQ measures 11 primary personality traits that are believed to contribute to three higher-order dimensions: negative emotionality, positive emotionality, and constraint. As an abridged version of the MPQ, the PBYA measure includes the scales aggression, alienation, control, harm avoidance, stress reactivity, traditionalism, and well-being. In the current project, the stress reactivity scale was used to develop a neuroticism factor. The content for stress reactivity includes questions about being easily upset, having unaccountable mood changes, being nervous/tense, being prone to feeling guilty, being sensitive/vulnerable, and being worry-prone/anxious. The stress reactivity scale has been shown to be strongly convergent with neuroticism, as defined by the Big Five (Hankin, Lakdawalla, Carter, Abela, & Adams, 2007; Tellegen & Waller, 2008). In the PBYA, many items are reverse-coded such that higher primary scale scores denote higher trait levels. Chronbach's alphas for the scales and the in the current sample range from .86–.92, suggesting that the internal consistencies are good and the majority of variance of any scale is shared.

Personality Inventory for DSM-5 (PID-5): The PID-5 is a 220-item questionnaire with a 4-point response scale (0, *Very false or often false*, to 3, *Very true or often true*) and was developed to measure the proposed *DSM-5* traits pathological personality traits (Krueger et al., 2012). While the majority of the items reflect greater levels of personality pathology, seventeen (approximately 8%) of 220 items are reverse coded. The PID-5 has 25 primary scales that have been reported to load onto five higher order dimensions (negative affect, detachment, antagonism, disinhibition, and psychoticism), which in turn map onto maladaptive poles of the Big Five personality dimensions. In the current project, one of the five higher order dimensions of the PID-5, negative affect was used to develop a neuroticism factor. The content for negative affect includes the lower order facets: anxiousness, emotional lability, hostility, perseveration (lack of) restricted affectivity, separation insecurity, depressivity, suspiciousness, and submissiveness (Krueger et al., 2012). The negative affect domain has been shown to be strongly convergent with neuroticism, as defined by the Big Five (De Fruyt et al., 2013; Gore & Widiger, 2013). Though some definitions of PID-5 negative affect use fewer facets (e.g., just using anxiousness, separation insecurity, emotional lability), a secondary goal of the current project was to examine theoretical aspects of neuroticism, withdrawal and volatility. These theoretical aspects map on to features of negative emotionality, as defined using the MPQ, for the three-factor model (Deyoung et al., 2007; Patrick et al., 2002). As such, using a broader neuroticism dimension made it possible to examine hypothesized aspects and their relationship to patterns of brain activation.

Krueger et al. (2012) provides psychometric details in large treatment-seeking and representative community samples. Chronbach's alphas for the 25 primary scales and the

higher order dimensions in the current sample range from .68–.95, suggesting that the internal consistencies are adequate to good and the majority of variance of any scale and the higher order dimensions is shared. Two validity items unlikely to be endorsed were embedded within the PID-5 to ensure careful responding (e.g., "I have never seen a tree"). Because there were no invalidity items in the other two measures (IDAS-II or PBYA), but all three measures were typically completed during the same assessment session, if a participant failed to properly answer the PID-5 validity items properly (i.e., "very false or often false"), their data for all three personality measures was removed from the final dataset. In total, N =25 participants were removed from the sample based on these criteria (See Figure 1, Consort Diagram).

Scoring and Norming the Personality Measures:

Based on the instructions delineated in the PID-5, facet and domain-level scores were only calculated if at least 75% of items for a given facet or domain were completed (American Psychiatric Association, 2013). This same rule was also applied to the IDAS-II scales and the PBYA facets, though not explicitly specified in the instructions, to ensure continuity across measures. Participants were excluded if they did not have sufficient domain scores to derive factor scores through a factor analysis (N=50, See Figure 1, Consort Diagram). To calculate negative affect from the PID-5, and so that no facet was overly represented, items from the contributing facets were averaged (emotional lability, anxiousness, restricted affect, separation insecurity, submissiveness,

hostility, perseveration, depressivity, and suspiciousness). Scores on restricted affect were reverse coded.

Before performing any data reduction analyses on the personality data, data were cleaned and prepared in SPSS Version 24. Because the maladaptive traits in the PID-5 and symptoms of anxiety and depression from the IDAS-II are unlikely to be endorsed in a normative population, PID-5 negative affectivity and IDAS-II dysphoria were positively skewed. Additionally, even though developed for a normative sample, nonetheless, stress reactivity from the PBYA was also positively skewed, according to the Kolmogorov–Smirnov (KS) test. To correct for robust positive skew, the Blom transformation, a rank-based transformation, was applied to IDAS-II dysphoria, PBYA stress reactivity, and PID-5 negative affect (Blom, 1958). Regression analyses were conducted to control for the linear effects of age and sex. This decision was based on previous studies which have shown age and gender based differences in rates of neuroticism.

Self-Report Data Reduction:

For use in both the psychoneurometric model and the fMRI analyses, a neuroticism factor score was derived from the self-report measures. These analyses were conducted in R (R Core Team, 2015) using a variety of analytic software packages such as psych, MASS, GPArotation, and lavaan. After examining correlations between the three self-report neuroticism measures, an exploratory single-level factor analysis was conducted on the three measures. The factor scores from this factor were extracted and

included as covariates in subsequent fMRI analyses, in order to determine whether neuroticism related to the hypothesized neural markers of interest.

Additionally, based on research which suggests that neuroticism contains distinct aspects (volatility and withdrawal), a two-factor exploratory factor analysis was conducted on the following items: PID-5 emotional lability, PID-5 anxiousness, PID-5 separation insecurity, PID-5 depressivity, PID-5 submissiveness, PID-5 suspiciousness, PID-5 hostility, PID-5 perseveration, PID-5 (lack of) restricted affectivity, PBYA-stress reactivity, PBYA-alienation, PBYA-aggression, and IDAS-II dysphoria. Results of this factor analysis reveal two-factors which map onto previous research on aspects of neuroticism. One difference in the current project is that perseveration loads onto the withdrawal factor, even though previous research has found preservation to load onto a the volatility factor (Deyoung, Carey, Krueger, & Ross, 2016). The results of this EFA are reported in Table 2. The factor scores from these two factors were extracted and included as covariates in subsequent fMRI analyses, in order to determine whether aspects of neuroticism were differentially related to the hypothesized neural markers of interest.

fMRI Task:

During the fMRI scan session, participants completed an emotion processing task adapted from Hariri and colleagues (Hariri et al., 2002). The task has been shown to reliably activate the amygdala in response to negative emotion viewing (Sauder, Hajcak, Angstadt, & Phan, 2013). During the task, participants completed blocks of emotional

faces and shape trials. During the blocks of emotional face-matching trials, participants would see an emotional face at the top of the screen and would have to choose (by pressing a button on the button box) which of two emotional faces displayed at the bottom of the screen matched the emotion of the face at the top of the screen. During the blocks of shape-matching trials, participants would see a shape at the top of the screen and would have to choose which of two shapes displayed at the bottom of the screen matched the shape at the top of the screen. In this version of the task, the faces displayed have either angry or fearful faces. Emotion trials were blocked together and shape trials were blocked together. Each 30-second block consisted of 6 5-second trials of that task type (emotion or shape) and the entire task consisted of 4 emotion blocks and 4 shape blocks. In addition, there were 3 20-second control blocks in which participants saw a fixation cross for 5-seconds and were instructed to press a key on their button box. The task was 5 minutes long. Stimulus presentations and response recordings were performed using E-prime (Psychological Software Tools, Pittsburgh, PA). An image of the task is displayed in Figure 2.

fMRI Acquisition and Pre-processing:

Imaging was performed using 3T Siemens Trio and Prisma MRI Scanners at the Center for Magnetic Resonance Research (CMRR) at the University of Minnesota. Images were collected with a 32-channel head coil and vacuum pillow in order to reduce head motion. High-resolution anatomical scans were collected and are used in the current study for localization of function. The images were acquired using the following

sequence: MPRAGE, TE = 3.65 ms, TR = 2530 ms, flip angle = 7 degrees, FOV=256mm, matrix=256×256, in-plane resolution = 1.0 mm × 1.0 mm, slice thickness = 1 mm, 240 slices, acceleration factor of 2 (GRAPPA). During the structural scan, participants watched a movie of their choice, listened to music, or chose to wear earplugs with no input. Each participant's structural scan was reviewed for radiological abnormalities. If study staff believed that the scan might be atypical, the results were sent to the Department of Radiology for follow-up. Any scans that had clinically significant findings were removed from the final data-set. Additionally, participants who did not have clinically significant radiological abnormalities but who nonetheless had brain deviations that were deemed by study staff to be significant enough to potentially alter brain functionality (e.g., sizable cysts) were excluded from the final sample. In total, *N* =32 participants were removed from the sample based on these criteria (See Figure 1, Consort Diagram). Additionally, N=7 participants were removed from the sample because of problems associated with the functional MRI task (e.g., the task did not start properly, the participant was unable to see the task due to poor eyesight).

A mirror on the head coil enabled subjects to view the behavioral task projected onto a rear-projection screen at the head of the scanner bore. Functional scans were collected on the Trio and Prisma scanners using a T2*-sensitive echo planar sequence (EPI, TE = 28 ms, TR=2.5s, flip angle=90◦, FOV=200mm, matrix=64×64, slice thickness=3.1mm with a 20% gap, in-plane resolution = 3.1 mm × 3.1 mm, 43 transversal slices, interleaved slice acquisition). The phase encoding direction was posterior to anterior. Immediately prior to acquiring the task data, a short, 10-volume echo-planar scan was collected using the same parameters and positioning as the task data, but with

opposite phase encoding (anterior to posterior). This opposite phase encoded scan was later used to correct geometric distortions in the task data.

Functional data was analyzed using FMRIB's Software Library (FSL 5.0.9; www.fmrib.ox.ac.uk/fsl/). Each functional data set was registered to the relevant anatomical dataset using a rigid-body linear transformation, and each participant's anatomical data were registered to a standard coordinate space (Montreal Neurological Institute's MNI 152 2-mm volume) using a full affine transformation to allow cross subject comparisons in a common space.

Functional data was preprocessed using the following steps: motion correction using the first volume in the functional series as the reference volume; slice timing correction; skull stripping; spatial smoothing using a 6 mm FWHM Gaussian filter; grand-mean scaling; and high-pass temporal filtering with a 100s cutoff. Additionally, geometric distortion correction using FSL's topup and applytopup were used. For this process, the first 10 images from the task data were extracted from the data set. They were combined with the 10 images from the AP data set and submitted to topup to create an unwarping field. That unwarping field was then applied to the full task data set to produce an unwarped data set. After preprocessing, each participant's data run was evaluated for excessive motion using a tool in FSL, fsl_motion_outliers, which detects time points in an fMRI dataset that have been corrupted by large motion (any volume in the 75^{th} percentile + 1.5x the interquartile range). The default metric was utilized, which involves examining the root mean squared (RMS) intensity difference of volume N relative to the reference volume. No participants showed motion outliers on greater than 25% of the volumes (the pre-determined exclusion cut-off); as such, no participants were

excluded for excessive motion. Additionally, a covariate of non-interest file was produced for each subject which included the three linear and three rotational motion estimates produced by the motion correction step**.**

Brain masks were prepared for use in subsequent data extraction and small volume correction analyses. A mask for the amygdala, defined anatomically by the Harvard-Oxford Subcortical Atlas, was constructed and constrained using a post-interpolation threshold of 0.7. Based on previous studies which have found altered neuroticism to be associated with activation in the medial PFC as well as altered connectivity between the amygdala and the medial PFC, a medial PFC region of interest was selected using coordinates from a study of the regulation of negative emotions (Diekhof, Geier, Falkai, & Gruber, 2011) This region in the ventral-medial PFC (vmPFC) is the result of a coordinate-based quantitative meta-analysis on 49 studies examining neural correlates of emotion regulation in response to negative emotions. Additionally, in the meta-analysis, the authors found that down-regulation of emotion in this region was associated with reduced activation in the amygdala, suggesting that it might be a central hub for amygdala-cortical emotion regulation circuitry. Using FSL, a spherical mask of the region identified by Diekhof and collagues was constructed, with an 8 mm radius around the coordinate.

Subject and Group level fMRI Task Analyses:

Magnitude of Amygdala Activation

Preprocessed data from each subject was submitted to three separate subject-level GLMs. The first GLM measured magnitude of amygdala activation across the task. In this model, two predictors of interest were included: shape and emotion. Fixation was not modeled, in order to serve as a neutral baseline. The task predictors were convolved with a prototypical gamma-function approximation of the hemodynamic response. The temporal derivative for each task predictor was also added to the model. Predictors of no interest included three linear translation and three rotation motion predictors, as well as nuisance predictors for each volume that exceeded the motion criteria. Task predictors were coded as the start and duration of all of the emotion and shape portions of the task. All task predictors were coded in seconds. The contrast of interest compared activation during emotion blocks to activation during shape blocks. Subject specific parameter estimates for the activation in the amygdala and vmPFC masks, described above, was extracted from the emotion>shape contrast using the featquery tool found in FSL for use in the psychoneurometric model.

Next, the within-subject output from the first subject-level GLM was passed to two separate group-level GLM's, one comprised of first-born twins and one comprised of second-born twins. Three regressors were included in these analyses: group mean, each individual's neuroticism factor score, and a regressor for scanner type (Prisma or Trio), to control for the fact that two different scanner types were used over the course of the study and participants were therefore scanned on different scanner types (Han et al., 2006; Jovicich et al., 2009). These analyses produced mean statistical maps of the emotion>shape contrast, for each twin group. Using a small-volume correction with the amygdala (defined anatomically using the Harvard-Oxford Subcortical Atlas), these

statistical maps were cluster-thresholded at $z=2.3$, $p<.05$. An additional secondary analysis was conducted using the same parameters and twin groups but, instead of the amygdala, the small-volume correction was conducted with the vmPFC mask (described above).

Habituation of Amygdala Activation

The second GLM measured habituation of amygdala activation over the course of the task. In this model, 5 predictors of interest were included: 1 shape predictor (accounting for all 4 shape blocks) and 4 emotion predictors (a separate one for each emotion block). A variation on the model was run using 8 predictors of interest, 4 shape predictors (a separate one for each shape block) and 4 emotion predictors. The results from these two different models (5 predictors vs. 8 predictors) did not significantly differ, so the first model (with 5 predictors) was used for subsequent analyses. The task predictors were convolved with a prototypical gamma-function approximation of the hemodynamic response. The temporal derivative for each task predictor was also added to the model. Predictors of no interest included three linear translation and three rotation motion predictors, as well as a nuisance predictor for each volume that exceeded the motion criteria. Task predictors were coded as the start and duration of each of the four emotion blocks and all of the shape blocks. All task predictors were coded in seconds. Two contrasts of interest were examined: one which examined the positive linear trend of the data and one which examined the negative linear trend of the data (habituation). The first contrast tests the change in relative difference in the magnitude between emotion

blocks and fixation block (baseline) across the four emotion blocks, assuming that the response to emotion increases over time and that the difference grows across blocks at roughly the same rate. The second contrast tests the same theory except models the response to emotion decreasing, relative to fixation, across blocks (modeling habituation). Subject specific parameter estimates for the change in activation in the amygdala and vmPFC were extracted from the positive trend and negative habituations contrasts using the featquery tool found in FSL for use in for use in the psychoneurometric model.

Next, the within-subject output was passed to two separate group-level GLM's, one comprised of first-born twins and one comprised of second-born twins. Three regressors were included in these analyses: group mean, each individual's neuroticism factor score, and a regressor for scanner type (Prisma or Trio). These analyses produced mean statistical maps of the change in activation over time, relative to fixation. Using a small-volume correction with the amygdala, these statistical maps were cluster-thresholded at $z=2.3$, $p<.05$. An additional secondary analysis was conducted using the same parameters and twin groups but, instead of the amygdala, the small-volume correction was conducted with the vmPFC mask (described above).

Amygdala-vmPFC PPI Analysis

The third GLM measured amygdala-vmPFC connectivity during task relevant conditions (emotion>shape) using a psychophysiological interaction (PPI). Psychophysiological interactions measure the relationship between activity in a seed

region and activity throughout the entire brain (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). It is one of the primary ways to measure task-relevant functional connectivity. Based on the previous literature, the amygdala was selected as the seed region. In order to conduct the PPI, the anatomical amygdala was transformed into each participant's functional space using the FLIRT tool found in FSL. The mean time-series for the amgydala was extracted for each individual (using the fslmeants tool found in FSL). Subject level connectivity analyses were conducted using the FEAT tool in FSL. Using the same preprocessing as above, three task predictors were included in the model: 1) a single task predictor for the start and duration times for all emotion and shape blocks (where emotion blocks were coded with a 1 and shape blocks were coded with a -1, to indicate the emotion>shape contrast), 2) a task predictor with each individual's amygdala mean time-series, and 3) a task predictor quantifying the interaction between the amygdala time-course and the emotion>shape contrast. The contrast of interest results from the interaction between amygdala time-course and the emotion>shape contrast. This analysis identifies regions that display stronger functional connectivity (or task-related co-activation) with the amygdala for negative emotional faces compared to the shape condition. Subject specific parameter estimates for the relationship between the amygdala and vmPFC time courses were extracted from masked vmPFC using the featquery tool found in FSL for use in the psychoneurometric model. This connectivity value represents the strength of the correlation between the amygdala time-course and the vmPFC time-course during the emotion>shape contrast of the task.

Next, the within-subject output was passed to two separate group-level GLM's, one comprised of first-born twins and one comprised of second-born twins. Three

regressors were included in these analyses: group mean, each individual's neuroticism factor score, and a regressor for scanner type (Prisma or Trio). These analyses produced mean statistical maps of regions showing greater connectivity with amygdala during the emotion blocks relative to the shape blocks. Using a small-volume correction with the vmPFC, these statistical maps were cluster-thresholded at $z=2.3$, $p<.05$.

Neural-Marker Data Reduction

For use in the psychoneurometric model, a neuroticism factor score was derived from the neural-markers. These analyses were conducted in R (R Core Team, 2015) using a variety of analytic software packages such as psych, MASS, GPArotation, and lavaan. After examining correlations between the three self-report neuroticism measures, an exploratory single-level factor analysis was conducted on the three measures.

Withdrawal and Volatility Group Analyses:

Based on previous literature which has suggested that inconsistencies in the literature examining neural correlates of neuroticism might be resulting from the multi-faceted nature of the neuroticism construct (Allen & Deyoung, 2015), the three GLMs reported above were replicated using the volatility and withdrawal factor scores described above. All methods remained consistent, aside from including the two regressors (withdrawal and volatility) in the models, instead of the single neuroticism factor score regressor.

Gender-based Group Analyses:

Additionally, based on previous literature which has suggested that inconsistencies in the literature examining neural correlates of neuroticism might result from the fact that neuroticism and possibly patterns of brain activation vary across genders (Ormel, Bastiaansen, et al., 2013), the three primary neuroticism GLMs reported above were replicated but the twin groups were further sub-divided by gender. All methods remained consistent and the analyses were examined in four groups (first-born females, first-born males, second-born females, second-born males; See Figure 1, Consort Diagram).

Whole-Brain Analyses by Twin Group:

Though the primary interest in the functional data concerned the relationship between task activation, habituation, and connectivity and measures of neuroticism, it was important to confirm that the output of the three task-based GLM analyses appeared to be activating or co-activating similar brain regions as had been found in previous studies using the task. To examine this, the within-subject output from each of the three GLMs were passed to two separate group-level GLM's, one comprised of first-born twins and one comprised of second-born twins (for a total of 6 group level GLMs). These analyses produced mean statistical maps of the 1) mean activation in the task during the emotion>shape contrast, 2) positive and negative trend of whole brain habituation over

the course of the four emotion blocks compared to shape 3) amygdala-whole brain connectivity during the emotion>shape contrast. The two group-level GLM maps for each task analysis were examined visually to ensure that the maps for both twin groups appeared similar to one another and to published reports of similar analyses (See Figure 5).

Psychoneurometric model:

The results section presents associations of self-report, fMRI-derived, and joint self-report/fMRI-derived (psychoneurometric) conceptualizations of Neuroticism. Zero-order correlations (Pearson's r) are reported to provide a picture of relationships among neuroticism scores (IDAS-II dysphoria, PID-5 negative affect, and PBYA-stress reactivity) and neural indicators (amygdala activation, amygdala habituation, amygdala-vmPFC connectivity) at a basic bivariate level. A series of single level, higher-order, and hierarchical (bifactor/Schimid-Leiman) factor analyses models incorporating scores on neuroticism measures along with hypothesized neural indicators of neuroticism were attempted. The goal of these analyses was to establish a well-fitted model with a psychoneurometric factor.

The two theoretical models explored for the relationship between the neural and personality data are the hierarchical and higher-order models. If the hierarchical model (or bifactor model) best characterizes the data, there would emerge a general psychoneurometric neuroticism factor that would saturate all of the scales. The specific self-report measure scales and neuroscientifically-derived markers, though, would be

saturated with the general psychoneurometic neuroticism factor, as well as the measurement domain factors (e.g., psychological scales would be saturated with psychological factor, neuroscientifically-derived markers would be saturated with the neural factor). These two measurement-specific factors would not be correlated with one another. This model would indicate that the model is saturated by the broad psychoneurometric model, but that the specific scales and markers are saturated by their measurement specific factors, which vary independently of the general factor. This is the model that the current project hypothesizes would best capture the data.

If the alternative theoretical model, the higher-order model, best characterizes the data, there would emerge a general psychoneurometric neuroticism factor. This factor would bifurcate into distinguishable factors (psychological neuroticism and neuroscientifically-derived neuroticism) that would then be further sub-divided into the specific self-report scales and neural markers. In this model, the correlations among the scales would be accounted for by the two higher-order sub-factors (psychological and neuroscientifically-derived neuroticism) and the relationship between the sub-factors would be explained by the overarching factor. Both of these hypothesized models are depicted visually in Figures 6b and 6c.

Results

Personality Data Reduction:

In advance of the fMRI analyses and the psychoneurometric modeling, inter-and intra-method Pearson correlations were established between the primary hypothesized indicators of neuroticism (i.e., three self-report measures and three neural indicators

[amygdala activation, amygdala habituation, amgydala-vmPFC connectivity). Correlations among the self-report measures were moderate to strong. The correlation between PID-5 negative affect and IDAS-dysphoria was moderate (r=.478, p<.001), between PID-5 negative affect and PBYA-stress reactivity was strong (r=.788, p<.001) and between PBYA-stress reactivity and IDAS-dysphoria was moderate (r=.541, p<.001). Correlations among the neural variables, on the other hand, were very weak. The correlation between the magnitude of amygdala activation and amygdala habituation was very weak (r=-.064, p=.117), between amygdala activation and amygdala-vmPFC connectivity was very weak (r=-.118, p=.003), and between amygdala-vmPFC connectivity and amygdala habituation was very weak (r=-.070, p=.086). Correlations between the neural variables and the self-report variables were also very weak, ranging from -.008 to.04. The correlations between amygdala magnitude and the three self-report measures (PID-5-negative affect, PBYA-stress reactivity, and IDAS-dysphoria) were non-significant (all p's>.091). The correlations between amygdala habituation and the three self-report measures (PID-5-negative affect, PBYA-stress reactivity, and IDAS-dysphoria) were non-significant (all p's>.188). The correlations between amygdala-vmPFC connectivity and the three self-report measures (PID-5-negative affect, PBYA-stress reactivity, and IDAS-dysphoria) were non-significant (all p's>.603). The results of these correlations are visually depicted in Figure 3.

A single factor, exploratory factor analysis of the self-report personality variables revealed a neuroticism factor. Factor loadings are reported in Table 1a. A single factor, exploratory factor analysis of the neural variables failed to reveal a clear neural factor, likely due to the low correlations among the neural variables. Though there were not

enough indicators to further test this, a two-factor model was evaluated using the three neural indicators, revealing one factor including amygdala magnitude and connectivity and a second factor including amygdala habituation. Factor loadings are reported in Table 1b.

Patterns of Neural Activation

Figure 5 presents group-wise maps in the first-born and second-born twins for each of the three neural analyses (activation, habituation, and connectivity). Results reveal similar patterns of activation across both twin groups and compared to published reports of previous studies using similar methods in similar fMRI tasks (Breiter et al., 1996; Phan, Wager, Taylor, & Liberzon, 2002; Roy et al., 2009; Wedig, Rauch, Albert, & Wright, 2005). These findings suggest that both the task performance and the fMRI processing and analyses result in group-wise patterns of activation/connectivity that are comparable to data that has been used in previous studies. They also suggest that twin groups are activating similarly to the task, suggesting consistency in methods of analysis across participants.

A summary of the results of the various analyses conducted in FSL to determine associations between neuroticism, aspects of neuroticism, and gender differences in relationship to hypothesized neural markers and neuroticism can be found in Table 3 (and are reported below).

In order to determine whether there is an association between neuroticism and the hypothesized neural markers of interest, GLM models were run, using three predictors:

group mean, scanner, and factor scores for the neuroticism factor. Across both twin groups, there was no significant association between trait neuroticism and amygdala activation or habituation. An exploratory analysis found no significant association between activation in the vmPFC (as defined by coordinates from Diekhof, Geier, Falkai, & Gruber, 2011) and neuroticism. In the first-born twin group, there is a significant association between a negative trend of habituation in the vmPFC and neuroticism. This finding did not rise to the level of significance in the second twin group, but examining the data reveals evidence of a sub-threshold, non-significant association between habituation in the vmPFC and neuroticism. The results of the PPI analysis reveal a positive correlation between neuroticism and amygdala-vmPFC connectivity. This finding replicates across both twin groups.

In order to determine whether there might be differences in results associated with the aspects of neuroticism, similar GLM models were run, using four predictors: group mean, scanner, factor scores for withdrawal-like factor, and factor scores for volatility-like factor. There was no significant association between the aspects of neuroticism and amygdala activation or habituation. There was a significant association between a negative habituation trend in the vmPFC and the withdrawal-like factor in the first-born twin group, but no association in the second-born twin group. Additionally, in the PPI analysis of amygdala-vmPFC connectivity, a significant association between the withdrawal factor was found in the in the first-born twin group, but this pattern of association was not found in the second-born twin group.

In order to determine whether there might be differences in the relationship between the various neural markers and neuroticism based on gender, the original GLM

models were rerun in samples divided by both birth order and gender. This resulted in four groups: first-born male and female twins, second-born male and female twins, each with 123, 152, 125, and 148 subjects, respectively. The results largely did not vary by gender. There were no significant findings for amygdala activation or amygdala habituation across either gender. In the PPI analysis of amygdala-vmPFC connectivity, a significant association with neuroticism was found in the first-born females, and the second born male and female twins, but not in the first born male twins. Nonetheless, these patterns suggest that the current findings are likely not a result of a gender effect on the patterns of brain activation associated with neuroticism.

Psychoneurometric model

The second aim of the current study involved developing a model of neuroticism that included both self-report measures and hypothesized neural markers from fMRI. Typically, psychoneurometric models involve building exploratory single-level models using the multiple indicators across measurement domains followed by hierarchical (bifactor and Schmid-Lieman) and higher order models to test various theories about the relationship between the variables.

The results of the exploratory single level factor analysis of the psychological data reveal a strong psychological factor, capturing the shared variance across measures and indicating a neuroticism variable across the three self-report measures (Table 1a). Two exploratory single level factor analyses of the neural data were conducted. One included the magnitude of amygdala activation, habituation of amygdala activation, and amygdala-vmPFC connectivity (Table 1b). The other included magnitude of vmPFC activation,

habituation of vmPFC activation, and amygdala-vmPFC connectivity. Neither of these models resulted in a viable single factor neural variable, suggesting that there is no single neural factor across the neural measures used, and further indicating that there was unlikely to be a shared variance associated with neuroticism across the three neural measures. As a result, efforts to conduct subsequent modeling using these variables failed to produce a viable model.

After attempting factor analysis using minimum residuals factoring method, alternative factoring methods were utilized. Both principal factor solution and maximum likelihood factor analysis revealed similar findings, suggesting that a single factor solution did not fit this data. To determine whether these results might be driven by a few specific participants, models were rerun with the sample split randomly and by twin group (first-born and second-born twins). Modifying the data in these ways did not yield a single factor solution.

Because there was no single factor solution, the subsequent models (bifactor/ schmid-leiman, and higher-order) using the variables included in the current study failed to produce viable models. Appendix A includes the code employed for building these models in R Studio.

Discussion

The goals of the current project were twofold and followed from one to the next. The first aim was to determine whether specific neural markers (amygdala activation, amygdala habituation, and amygdala-vmPFC connectivity) derived from task-based

fMRI during negative emotion processing were consistently related to trait neuroticism, as defined using multiple self-report measures. These neural markers were selected based on previous literature, much of which has been limited by small sample sizes and inconsistent results. In the current study, using a large sample (N=663), it was possible to bring clarity to the question of whether there are certain patterns of brain activation derived during negative emotion processing that are consistently associated with the broad personality domain of neuroticism. The study design in the current project allowed for a within-study replication, by reproducing results found in a group of first-born twins in a different group of subjects consisting of the second-born twins from the pair. Though not based on independent samples, nonetheless, this method strengthened the conclusions from this project, as findings are generally consistent across the first-born and second-born twins. The second aim of the current project was to determine whether, using these neural markers and the self-report measures, it would be possible to improve the latent construct of neuroticism using measures derived from multiple measurement domains (i.e., a psychoneurometric model).

Overall, for the first aim of the project, of the three neural markers hypothesized to be associated with neuroticism, we found a positive association between trait neuroticism and amygdala-vmPFC connectivity in both twin groups. In the current study, we failed to find an association between trait neuroticism and magnitude or habituation of amygdala activation during negative emotion processing. Secondary analyses were conducted examining magnitude of activation and habituation in the vmPFC and neuroticism, based on studies which have found significant associations between these neural markers and neuroticism. Evidence from these secondary analyses found an

association between vmPFC habituation and trait neuroticism in the first-born twin group, while there was a trend level association in the second-born twin group. In these secondary analyses, there was no association between vmPFC activation and neuroticism in either twin group. Because the hypothesized neural markers did not show significant associations to one another or to the neuroticism self-report measures, it was not possible to build the theoretical psychoneurometric model. Suggestions for future markers to include in a psychoneurometric model of neuroticism using fMRI and related data will be reviewed below.

Magnitude of Amygdala Activation

The non-significant association between magnitude of amygdala activation and trait neuroticism in the current study adds support to the recent meta-analysis that also did not find this association across 18 studies looking at neuroticism and brain activation during emotion processing tasks (Servaas et al., 2013). Servaas and colleagues suggest that while the amygdala plays an important role in threat detection in response to salient stimuli in the environment, the regions which show alterations across the studies in the meta-analysis are those involved in fear learning (e.g., hippocampus and parahippocampus), anticipation of aversive stimuli (e.g., anterior cingulate cortex, posterior cingulate cortex) and emotion processing (e.g., middle cingulate gyrus, dorsal medial prefrontal cortex). Servaas and colleagues offer a model of the relationship between neuroticism and neural activation, based on the findings of the meta-analysis, in which individuals high in neuroticism have an over-active fear learning system coupled

with difficulties anticipating or predicting negative outcomes. This combination of neural patterns of activation results in uncertainty and higher levels of stress, or a 'neurotic cascade' (Suls & Martin, 2005), which is characterized by increased daily problems, higher emotional reactivity to these problems, more mood "spillover" from previous problems, and stronger emotional reactions to recurring problems. As a result of this increased emotional reactivity, there is a need for greater regulatory control in individuals higher in neuroticism. In such a model, the neural activation patterns associated with neuroticism might be better conceptualized as relating to the brain systems involved in down-regulating emotions, as opposed to primarily emotion perception and lower-order systems, such as threat detection, centered in the amygdala (Haas et al., 2008; Lemogne et al., 2011; Williams et al., 2006).

Amygdala-vmPFC Connectivity

Though certain components of the model developed by Servaas and colleagues were not testable using the neural correlates derived in the current study, the current project does provide support for alterations in the third feature of Servaas and colleagues neural model of neuroticism, in which hypothesized alterations in regulatory processes partially account for individual differences in trait neuroticism. The results of the PPI analysis examining the co-activation of the amygdala and the vmPFC were significant, suggesting that the time courses of activation in these two brain regions are correlated and that this correlation is positively associated with individual differences in trait neuroticism. As the vmPFC-amygdala pathway is understood to be core to the neural

mechanisms associated with emotion regulation, the significant finding in both twin groups suggests that altered connectivity between brain regions with emotion perception and brain regions associated with emotion regulation may central to the neural underpinnings of trait neuroticism (Delgado, Nearing, LeDoux, & Phelps, 2008; Phelps & LeDoux, 2005; Stein et al., 2007).

Previous studies using fMRI and resting-state fMRI (rsfMRI) provide support for this pattern of neural connectivity, in samples of healthy individuals, associated with individual differences in trait neuroticism. One study showed that, in healthy individuals, exposure to social stress was related to increased functional connectivity between the amygdala and the medial PFC during rs-fMRI, relative to individuals who were not exposed to stress (Veer et al., 2011). Another task-based fMRI study during negative emotion processing, also in a healthy sample, found that individuals with the short (s) allele of the human serotonin transporter gene (*SLC6A4*), a specific polymorphism associated with major depression, showed increased coupling of the amygdala and the vmPFC (Heinz et al., 2005). In a sample of healthy adolescents, increased coupling of the amygdala and the vmPFC (as well as the amygdala and the ACC and the dorsal-lateral PFC) was associated with trait neuroticism during fear learning (Tzschoppe et al., 2014).

Cremers and colleagues found that trait neuroticism was positively associated with amygdala and dorsal-medial PFC connectivity during angry and fearful face processing, though they found an inverse correlation between amygdala-ACC connectivity and neuroticism during sad face processing (2010). Another study found that individuals who had experienced early life stress during infancy showed increased levels of cortisol secretion during childhood, which was associated with decreased functional

connectivity between the amygdala and the vmPFC. These researchers, though, also found that positive vmPFC-amygdala connectivity was associated with symptoms of adolescent depression (and inversely correlated with adolescent symptoms of anxiety) (Burghy et al., 2012). In individuals with borderline personality disorder, a disorder which has been characterized as an extreme maladaptive version of neuroticism (Samuel, Carroll, Rounsaville, & Ball, 2013), increased vmPFC-amygdala connectivity was found during fear processing, suggesting a possible mechanism of exaggerated amygdala response, as the vmPFC may not be functioning in its inhibitory role over amygdala activity (Kamphausen et al., 2013).

Other possible explanations for this positive association between the amgydala-vmPFC and trait neuroticism and associated psychological features (such as depression) is that the process of emotion regulation involves a more effortful cognitive process in individuals higher in neuroticism and that the regulatory function may not be as effective at tempering amygdala reactivity, relative to in individuals lower in neuroticism (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Ochsner, Silvers, & Buhle, 2012; Urry, 2006). It may also be that this coupling reveals a more intertwined set of functional processes between the limbic emotion centers of the brain and the vmPFC, suggestive of more over-thinking, self-referential processing, and ruminating about emotional stimuli (Blair et al., 2008; Cremers et al., 2010; Disner, Beevers, Haigh, & Beck, 2011). These failures in neural processes of emotion regulation associated with neuroticism align with a relatively recent and growing understanding of transdiagnostic psychopathology, as in some part stemming from emotion dysregulation (Campbell-Sills & Barlow, 2007). The trend toward this thinking has been underscored by the growing

use of emotion regulation-based treatments for various forms of psychopathology (e.g., dialectical behavioral therapy, emotion-regulation skills, emotion-focused therapy (Berking et al., 2008; Gratz & Tull, 2010; Greenberg, 2017; Lynch et al., 2007). As such, the relationship among neuroticism, transdiagnostic psychopathology, and emotion dysregulation could be explained, in part, by alterations in this neural circuitry associated with emotion regulation.

Some studies that have examined the association between neuroticism and related psychiatric disorders have shown an inverse correlation between amygdala and vmPFC, and other brain regions in the prefrontal cortex. For example, similar to the finding from Burghy and colleagues (2012) reported above, another study found that during rs-fMRI, individuals with high anxiety showed negatively correlated vmPFC-amygdala connectivity, in contrast to individuals low in anxiety, who showed a positive correlation between amgydala-vmPFC connectivity (Kim, Gee, Loucks, Davis, & Whalen, 2011). Greater worry following an induction of perseverative cognition was predictive of a reduced connectivity during rs-fMRI between the amygdala and the vmPFC (Makovac et al., 2016). In a sample consisting of healthy individuals, individuals with depression, and individuals with PTSD, amygdala vmPFC connectivity was inversely correlated with depression symptoms but positively correlated with symptoms of anxiety (Satterthwaite et al., 2016). Taken together, these studies suggest a complex relationship between amygdala-vmPFC connectivity that depends on a variety of factors including the task, the sample group, the analytical methods, and the question being asked.

While some of these studies appear to contradict the PPI findings in the current project and the literature cited above, there are some possible explanations for these

divergent findings. First, across these studies the methods vary between task-based and rs- fMRI. Even among the tasks, the emotional stimuli vary. As Cremers and colleagues (2010) showed, neuroticism predicted increased coupling of the amygdala and prefrontal regions during angry and fearful stimuli but reduced coupling during sad stimuli, suggesting that the specific negative emotion induction influences the pattern of connectivity. Additionally, and perhaps more importantly, many of the studies above were measuring the amygdala-prefrontal connection in healthy individuals, and were looking at normal range differences in trait neuroticism. As in our sample, which is a community sample with relatively low rates of severe psychopathology, it may be that among individuals in the normal range of neuroticism, there is increased coupling between these brain regions as levels of neuroticism increase, suggesting increasingly more effortful, albeit generally successful, down-regulation of emotion. As the severity of psychopathology increases, these regions may no longer effectively communicate or successfully down-regulate emotions, which characterizes various psychiatric disorders across the spectrum (Kim & Whalen, 2009).

It is important to note that interpreting PPI findings can be difficult for several reasons. Because of how they are modeled, PPIs make the assumption that the task-relevant variance has been modeled and that what remains when there is a significant PPI is a correlation between activity in two brain regions, not accounted for by the modeled aspects of the task. In the current study, we used a block design for the emotion blocks and the shape blocks. The assumption made about these significant PPI findings is that the regions of interest (amygdala and vmPFC) are consistently active or inactive together during the emotion blocks. Significant PPIs, though, may be reflecting co-activation

between two regions for task-irrelevant reasons (O'Reilly et al., 2012). For example, it could be that the amygdala and vmPFC co-activate together when a new face image has been displayed, where perhaps both of these regions are activating independently to the novelty of the image, rather than acting together in response to the emotional content of the image. Additionally, PPIs can be difficult to interpret because they do not necessarily confer activation, but rather they confer an interaction between the time courses of two brain regions (or a seed region and the rest of the brain). It is hard to know with a PPI whether a significant finding is the result of two brain regions activating during the same task-relevant conditions, or possibly deactivating during task-relevant conditions.

Amygdala Habituation

In the current sample, no association between amygdala habituation and trait neuroticism was found. Only one previous study has found an association between neuroticism and habituation, and, as reviewed above, a limited number of studies have examined the association between habituation in various brain regions and psychopathology (e.g., ventral striatal habituation and depression; dlPFC habituation and borderline personality disorder). Habituation refers to the reduction in neural response to a repeatedly presented stimulus over time and it can be understood as a type neural regulatory process, as activation goes down as the brain grows accustomed to a certain stimulus (Thompson & Spencer, 1966). Though evidence has shown that amygdala reactivity is generally consistent over multiple scanning sessions to the same stimulus (Johnstone et al., 2005), research has suggested that within a scan session, amygdala

reactivity reduces with time to emotional stimuli (Breiter et al., 1996; Strauss et al., 2005). Breiter and colleagues found that the amygdala habituates rapidly, within one minute, to happy and fearful faces and that these habituation effects were maintained after an inter-stimulus delay of four minutes. Strauss and colleagues also found evidence of amygdala habituation in response to fearful faces, but they did not find this same effect in response to angry faces.

These findings highlight a few possible explanations for the non-significant association between amygdala habituation and trait neuroticism in the current sample. The emotional face-matching task employed in the current study was 5 minutes long and the four emotion blocks lasted for 30 seconds each. Within a block study design such as the one used in this study, it is difficult to parse change in activation over the course of the individual blocks, though the results from the study by Breiter and colleagues (1996) suggest that the lion's share of activation change may actually be occurring in that first block, rather than over the course of the task. Additionally, in the current study both angry and fearful faces were included within all four of the emotion blocks. Using the current analysis methods for a task using a block design, it is difficult to dissociate the findings based on the specific emotion. As such, it may be that including both of these different emotions is perhaps weakening the amygdala habituation findings, which may explain the non-significant association between amygdala habituation and trait neuroticism.

Additionally, in this project, the derived metric of amygdala habituation relies on the assumptions that the amygdala habituates in a linear fashion, in the same direction, and at the same rate over the course of the task. These assumptions follow from behavior

(e.g., people habituate to negative information over time [Foa & Kozak, 1986]) and physiology (e.g., heartrate and skin conductance in response to negative stimuli habituate over time in a linear fashion [Codispoti, Ferrari, & Bradley, 2006; Eckman & Shean, 1997]). Still, it is possible that activation in the amygdala could also habituate in a non-linear pattern, perhaps with activation in the amygdala habituating in a quadratic or cubic fashion. Plichta and colleagues (2014) provide an equation for quantifying amygdala habituation over the course of a task relying on a linear model, yet the graphs of the findings that they report in their study seem to indicate a possible non-linear, quadratic shape to amygdala habituation. Additionally, Schuyler and colleagues (2014) display average graphs of the time-course of the amygdala in their participants to negative emotional stimuli and the shapes of the curves suggest a quadratic pattern of habituation, and not a linear pattern. Furthermore, their measure of habituation was assessing the difference between initial reactivity against the recovery period, after the offset of the emotional stimulus. As such, their study makes no assumptions about the rate or shape of amygdala change over time. Both the study by Plichta and colleagues and by Schuyler and colleagues suggest that the linear model employed in the current study may not be accurately capturing the behavior of amygdala activation during negative emotion processing. Using the data employed in the current study, future analyses could probe the shape (e.g., linear vs. quadratic vs. cubic) of amygdala habituation in response to angry and fearful faces, in order to shed light on the pattern of amygdala reactivity to stimuli over time.

The current project did find preliminary evidence for an association between habituation of activation in the vmPFC and trait neuroticism, in that a significant

association was found for the first-born twin group and a trend-level association was found in the second-born twin group. Similar to the current study, Haas and colleagues (2008) did not find an association between amygdala activation over time and trait neuroticism but, contrary to the findings in the current project, they did find an association between sustained medial PFC activation during the presentation of sad facial expressions (but not fear or happy) and neuroticism. In the current study, the findings suggest an opposite pattern, with increased habituation in the vmPFC as neuroticism increases, in response to fear and angry emotional expressions. The vmPFC has been shown to play an important role in reducing aggressive behaviors in both human and animal studies (Davidson, Putnam, & Larson, 2000; Siegel & Edinger, 1983) and studies have found that sustained dorsal-medial PFC activation was associated with both fear and anger recognition (Pichon, de Gelder, & Grèzes, 2009). Activation in the vmPFC has also been associated with retention of extinction of fear learning over time (Phelps, Delgado, Nearing, & Ledoux, 2004). It may be that failure to sustain vmPFC activation in individuals higher in neuroticism suggests failure to regulate aggressive social behaviors and to suppress fear learning in situations of increasing emotional intensity, particularly with emotions such as anger and fear, each with strong urges to action.

Neural Correlates of Volatility and Withdrawal

Based on previous literature which has suggested that neuroticism might be dissociable into distinct aspects, withdrawal and volatility, a secondary aim of the current study was to determine whether these distinct aspects might have different association

with the hypothesized neural markers of interest (Cunningham, Arbuckle, Jahn, Mowrer, & Abduljalil, 2010). It has been suggested that these distinct aspects within trait neuroticism might be driving inconsistencies in the literature examining the neural correlates of trait neuroticism (Allen & Deyoung, 2016). Data reduction methods were employed to identify two factors of neuroticism, which supports the theory suggesting a withdrawal and volatility aspect of neuroticism (Deyoung et al., 2007). These distinct aspects were included in the three general linear models, with each of the three hypothesized neural markers. The results, though, were largely consistent across the withdrawal and volatility aspects, with no significant findings for either amygdala activation or habituation in either twin group for either aspect. This suggests that these neural markers, as measured in the current study, may not be indexing individual differences in the broader dimension of neuroticism or in the specific aspects of neuroticism.

Differences between the aspects were identified in amgydala-vmPFC connectivity (with the first-born twin group showing a significant association between withdrawal and amygdala-vmPFC connectivity) and vmPFC habituation (with the first-born twin group showing a significant association between withdrawal and vmPFC habituation). Because these findings do not replicate across both twin groups, it is important to interpret them cautiously. That said, Gray and McNaughton (2000) suggest that the behavioral inhibition system, which is more tightly linked with the withdrawal aspect of neuroticism, is centralized in the amygdala and hippocampus and underlies the passive avoidance that characterizes both anxiety and depression (DeYoung et al., 2016). While no differences were found in the amygdala activation or habituation, the vmPFC plays an important role

in promoting and regulating the functions of the amygdala. As such, the differences found with amygdala-vmPFC connectivity and habituation may explain aspects of the behavioral presentation that characterizes withdrawal (including rumination, perfectionism, interpreting ambiguous feedback as negative) (Randles, Flett, Nash, McGregor, & Hewitt, 2010). Volatility, on the other hand, is characterized by the action tendencies encompassed in the flight-fight-freeze system, which is believed to be controlled by lower-order neural systems (the amygdala, hypothalamus, the midbrain, and the motor and somatic nuclei of the brainstem) (Gray, 1982).

While there are subtle neural differences found across the aspects of withdrawal and volatility, the findings in the current study do not point to an easily distinguishable pattern of brain activation associated with volatility or withdrawal. Neuroticism, though, is by definition a higher order dimension associated with many lower order facets and, even when broken down into aspects, there are multiple features of these aspects likely associated with varied brain systems. Future studies looking at aspects of amygdala functioning, would likely benefit from using a more focal psychological construct that might be more closely linked with amygdala activation and habituation. For example, a more fundamental psychological trait hypothesized to be closely related to the function of the amygdala, such as fearfulness, might be more directly related to amygdala activation or habituation, and therefore might be better utilized in such a psychoneurometric model (LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Larson et al., 2006; Phelps & LeDoux, 2005; Sabatinelli, Bradley, Fitzsimmons, & Lang, 2005). Given the role that fearfulness plays in various forms of internalizing psychopathology, clarifying this relationship might serve as a better intermediary between psychopathology and functional

neuroimaging.

Additionally, in the current study, the personality measures employed to derive the neuroticism factor scores, to identify the neuroticism aspects, and to build the psychoneurometric model were not standard Big Five or Big Three measures. Rather, the PID-5 negative affect scale was designed to assess maladaptive personality traits and the IDAS-II dysphoria was developed to assess dysphoria associated with DSM-IV diagnoses of depression and anxiety. While evidence broadly finds that these measures are associated with normal range personality measures (Gore & Widiger, 2013; David Watson, Stasik, Ro, & Clark, 2013) nonetheless, due to their clinical focus, these measures might be failing to adequately characterize the range of neuroticism-like features in the community sample used in the current study.

Neural Correlates and Gender Differences

Previous studies on neural correlates of neuroticism have also suggested that inconsistencies in findings might be attributable to gender differences in both levels of neuroticism and in patterns of neural activation during negative emotion processing (Ormel, Bastiaansen, et al., 2013). In order to test this in the current sample, the twin-groups were sub-divided by gender. Each of these sub-samples had over 120 participants, making each of these samples substantially larger than the average study using fMRI. When the groups were sub-divided by gender, the results largely did not vary across gender, and no differences were found with amygdala activation or habituation. As amygdala activation is the most commonly studied functional neural marker in relation to

neuroticism (and the one in which the findings have shown the most inconsistencies), the current project does not lend support for the notion that accounting for gender differences might explain the contradictions in the literature. The only difference found across genders was a non-significant association between amygdala-vmPFC connectivity and neuroticism in the male, second-born twins (but this association was found in the male, first-born twins). This may be due to the fact that the effect size of this finding is not big and when the sample size is reduced, there is insufficient power to identify the association in male, second-born twins. Given the overall consistent findings across genders, it suggests that failure to replicate findings of previous studies in the current project is unlikely to be attributable to gender differences.

Psychoneurometric Model

Based on the hypothesis that the three neural markers chosen for the current project were likely to be significantly associated with neuroticism, the second goal of the project was to determine whether, using multiple measures across two measurement domains (fMRI and self-report) the construct of trait neuroticism could be refined. The findings from the first study aims, though, revealed that the hypothesized neural markers do not meaningfully relate to neuroticism, at least in the current sample (first-born twins) and the replication sample (second-born twins). Additionally, the three fMRI markers were not significantly correlated with one another, and did not produce a single factor using exploratory factor analysis (a condition for building the hypothesized psychoneurometric model). Therefore, it was not possible to successfully implement the

second aim of the project, to build a multi-method, multi-measure model of neuroticism. As such, the goal of using these multiple measurement types, in the current project, did not yield an improved neuroticism variable. Below, possible future directions are discussed and potential methods of using MRI metrics to build meaningful psychoneurometric models with neuroticism and other psychological constructs of interest are proposed.

Previous successful attempts to build psychoneurometric models have utilized physiological measures, such as startle or heart rate, or neural indicators such as event-related potentials (ERPs), including the P3 and the response-locked Error Related Negativity (ERN) derived from electroencephalography (EEG) (Venables et al., 2017; Yancey et al., 2015). The neural and physiological measures in both of these studies had consistently been shown to be associated with the constructs of interest (Patrick et al., 2013; Vaidyanathan, Patrick, & Bernat, 2009). In the current study, though, the fMRI markers selected for testing and inclusion in the model were based on inconsistent findings or few studies with small sample sizes.

Not only did the fMRI markers hypothesized for the current project not show consistent relationships with the psychological variables of interest, they were not meaningfully related to one another. Though this project hypothesized that the three neural markers of interest would cohere into a common factor, this was observed to not be the case. Instead what is observed in this study are three distinct signals, indexing different neural processes that may reflect differing cognitive processes. This may further the notion that activation, habituation, and PPI characterize fundamentally orthogonal methodological constructs. More research is needed to clarify the neural correlates of

emotion regulatory processes and how they may or may not relate to one another.

Generally, using fMRI, it has proven more difficult to identify consistent markers of psychopathological constructs relative to self-report measures and clinical observation. Due to methodological issues such as small sample sizes and stringent alpha-level corrections, correlations in cognitive neuroscience are likely to be artificially inflated (Yarkoni, 2009). As a result, a well-powered replication study such as the current project is relying on previous findings that are likely to be reflective of inflated relationships. A project such as the current one can go a long way in clarifying a muddled literature plagued by numerous, under-powered studies. Additionally, the current project highlights the importance of publishing null results in the literature. It is likely that more studies have failed to find an association between magnitude of amygdala activation and trait neuroticism than the ones that appear in the literature (Earp & Trafimow, 2015; Ferguson & Heene, 2012). This information would be invaluable for the current study, in which replicating previous findings was important for subsequently conducting a psychoneurometric model with this data.

While the need for replication studies and publication of null findings are important across the social sciences, in the world of fMRI research, there are specific challenges to replication as methods vary widely across studies. Even in two seemingly similar datasets, researchers make a myriad of decisions, from selecting the task to data preprocessing to setting up the statistical model, all of which further differentiate the findings across studies. This means that two studies which appear to be examining the same questions may employ very different fMRI methods and may come up with conflicting results (Poldrack et al., 2013). As such, larger sample sizes, multi-site studies,

and data-sharing efforts will be necessary for identifying consistent fMRI findings that can be used in follow-up analyses, such as for psychoneurometric modeling (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). For example, moving forward, it might be useful and advisable to continue using amygdala-vmPFC connectivity as a useful neural correlate of neuroticism. Such a variable, along with other well validated neural markers might produce a valid and informative psychoneurometric model for neuroticism.

In addition to identifying more consistent neural markers, another possible future direction for building a psychoneurometric model for neuroticism would be to employ metrics from other MRI modalities, such as structural and rs-fMRI. While personality is understood to be enduring and predictable across a variety of settings, there is evidence suggesting that fMRI findings may change depending on specific states or diagnoses. In the current study, we examined the neural correlates of neuroticism using various metrics of task-related brain activation. Research on individuals with depression have shown that post-treatment, using both therapy and medications, patterns of brain activation in response to emotional tasks change and typically activation decreases in regions associated with emotion processing (Anand et al., 2005; Dichter, Felder, & Moria Smoski, 2010; Sheline et al., 2001). Similar changes in patterns of brain activation after treatment have been found in individuals with diagnoses of panic disorder (Beutel, Stark, Pan, Silbersweig, & Dietrich, 2010; Kircher et al., 2013), borderline personality disorder (Perez et al., 2016), and generalized social phobia (Phan et al., 2013). Such findings suggest that fMRI during emotion processing may be less amenable for the study of more enduring, trait personality processes.

Further, the tasks employed in task-based fMRI are, by necessity, specific and narrow, and may fail to capture broad neural systems underlying personality domains (Adelstein et al., 2011). Studies have suggested that, for capturing aspects of the personality domains, rs-fMRI analyses which characterize the intrinsic brain activity in the absence of a task, such as independent components analysis or seed-based analyses, might effectively capture enduring neural elements that map on to stable personality domains. One study found that neuroticism predicted increased connectivity within the precuenous and between the precuneous and the dorsal-medial PFC. The authors interpret these findings as indicating tighter coupling between social and emotional information, suggesting higher conflict during socio-emotional situations. (Adelstein et al., 2011). Other studies have also used rs-fMRI and intrinsic connectivity methods to characterize trait neuroticism. While there is no consensus in the rs-fMRI literature, either, about the broad neural correlates of neuroticism, with larger sample sizes, this may be an effective way to characterize personality, given that it has been shown to be reliable (Wisner, Atluri, Lim, & Macdonald, 2013), it is amenable to multi-site study designs (Abraham et al., 2017), and it lacks the constraints of the particularities and peculiarities of specific tasks (Otten & Rugg, 2001).

Limitations

One thing that is important to note for the current study design is that within FSL's FMRIB software there is currently no tool for fitting biometrical models to twin data. This means that it is challenging to perform voxel-by-voxel comparisons between

activation in two twin groups, due to the enormous number of voxels in a whole brain analysis and, therefore, the resulting number of accompanying comparisons. Additionally, there is no way to correct for the non-independent data when all twins are included within one group analysis, such as clustering twin data within families, in current neuroimaging software. This was part of what motivated the replication study, as opposed to including all of the twins at in the same model. We believe that this is a strength of the current project, as each of the twin groups is much larger than the extant studies on amygdala activation, habituation, and connectivity associated with neuroticism. Still, the replication of findings from the first-born twin group to the second-born twin group does not represent a true replication study, as the twins are related and therefore non-independent data points. Nonetheless, showing the same or similar results in these two large samples inspires confidence about the validity of the reported results.

Conclusion

Overall, the current project finds evidence for a relationship between neuroticism and vmPFC-amygdala co-activation during negative emotion processing in two large samples, while failing to replicate a relationship between amygdala activation or habituation and neuroticism. These findings suggest that a key element in the neural underpinnings of neuroticism is related to the interplay between the vmPFC, a central brain region involved in emotion regulation and the amygdala, the brain region involved in emotion perception and processing. This highlights that a crucial mechanism underlying neuroticism may be a failure in emotion regulation, rather than a problem with

gating emotional information. This finding may help explain the utility of treatments focused on emotion regulation for various transdiagnostic mental illnesses, associated with elevated levels of neuroticism. This finding further suggests that focusing on mechanisms of emotion regulation in relationship to trait neuroticism might be fruitful for identifying additional neuroscientifically derived correlates.

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Table 1a. Exploratory Factor Analysis of the Psychological Measures of Neuroticism

Single-level Factor Analysis of Psychological Measures of Neuroticism		
Variable	**Loading**	**Communality**
PID-5 Negative Affectivity	0.83	0.70
PBYA Stress Reactivity	0.94	0.89
IDAS-II Dysphoria	0.57	0.33

Table 1b. Exploratory Factor Analysis of the Neuroscientifically-Derived Measures of Neuroticism

Single-level Factor Analysis of Neural Measures of Neuroticism		
Variable	**Loading**	**Communality**
Amygdala Magnitude	-0.11	0.0130
Amygdala Habituation	-.06	0.0039
Amygdala-vmPFC Connectivity	1.00	0.9960

Table 1a. Exploratory Factor Analysis of the Psychological Measures of Neuroticism.

The single factor, factor analysis of the three self-report measures revealed a single factor

representing the shared features across the measures that for this project is conceptualized as the neuroticism factor.

Table 1b. Exploratory Factor Analysis of the Neuroscientifically-Derived Measures of Neuroticism. The single factor, factor analysis of the three neural measures hypothesized to be associated with neuroticism failed to produce a single factor. The data suggests that a two-factor solution might better fit the data, though it is not possible to run such a model with only three indicators. These findings suggest that across these three neural markers in this sample, it is not possible to identify a neuroticism factor.

Table 2. Exploratory Factor Analysis of Neuroticism Variables: Primary and Secondary Loadings

Variables	Withdrawal (Variance explained = 32.0%)	Volatility (Variance explained = 18.0%)
PID-5 Emotional Lability	**0.84**	-0.18
PID-5 Anxiousness	**0.80**	0.04
PID-5 Hostility	*0.31*	**0.51**
PID-5 Separation Insecurity	**0.54**	0.07
PID-5 Suspiciousness	0.21	**0.55**
PID-5 Perseveration	**0.56**	0.27
PID-5 Submissiveness	**0.44**	-0.01
PID-5 Depressivity	**0.64**	0.25
PID-5 (lack of) Restricted Affectivity	0.19	**-0.62**
PBYA-Stress Reactivity	**0.83**	0.07
PBYA-Alienation	0.24	**0.61**
PBYA-Aggression	-0.05	**0.73**
IDAS-II Dysphoria	**0.58**	-0.07

Table 2. Exploratory Factor Analysis of Negative Affect Scales. Factor analysis of Negative Affect scales from the PID-5, PBYA, and IDAS-II revealed a two-factor solution suggesting a withdrawal factor and a volatility factor, in line with research conducted by DeYoung and colleagues (2007). As theory might suggest different brain systems underlying these aspects of neuroticism, follow-up analyses were conducted to determine whether distinct patterns of neural activation could be identified using these discrete factors of neuroticism.

Association Between Psychological Variables and Neural Variables in FSL Software

	Amygdala Magnitude		**Amgydala Habituation**		**Amygdala-vmPFC PPI**	
	Twin 00	Twin 01	Twin 00	Twin 01	Twin 00	Twin 01
Neuroticism Factor	X	X	X	X	**Present**	**Present**
Withdrawal Factor	X	X	X	X	**Present**	X
Volatility Factor	X	X	X	X	X	X
Neuroticism Factor (Males Only)	X	X	X	X	X	**Present**
Neuroticism Factor (Females Only)	X	X	X	X	**Present**	**Present**

	vmPFC Magnitude		**vmPFC Habituation**	
	Twin 00	Twin 01	Twin 00	Twin 01
Neuroticism Factor	X	X	**Present**	X (Trend)
Withdrawal Factor	X	X	**Present**	X
Volatility Factor	X	X	X	X

Table 3. Associations Between Psychological Variables and Neural Variables in FSL.

X's indicate no significant findings.

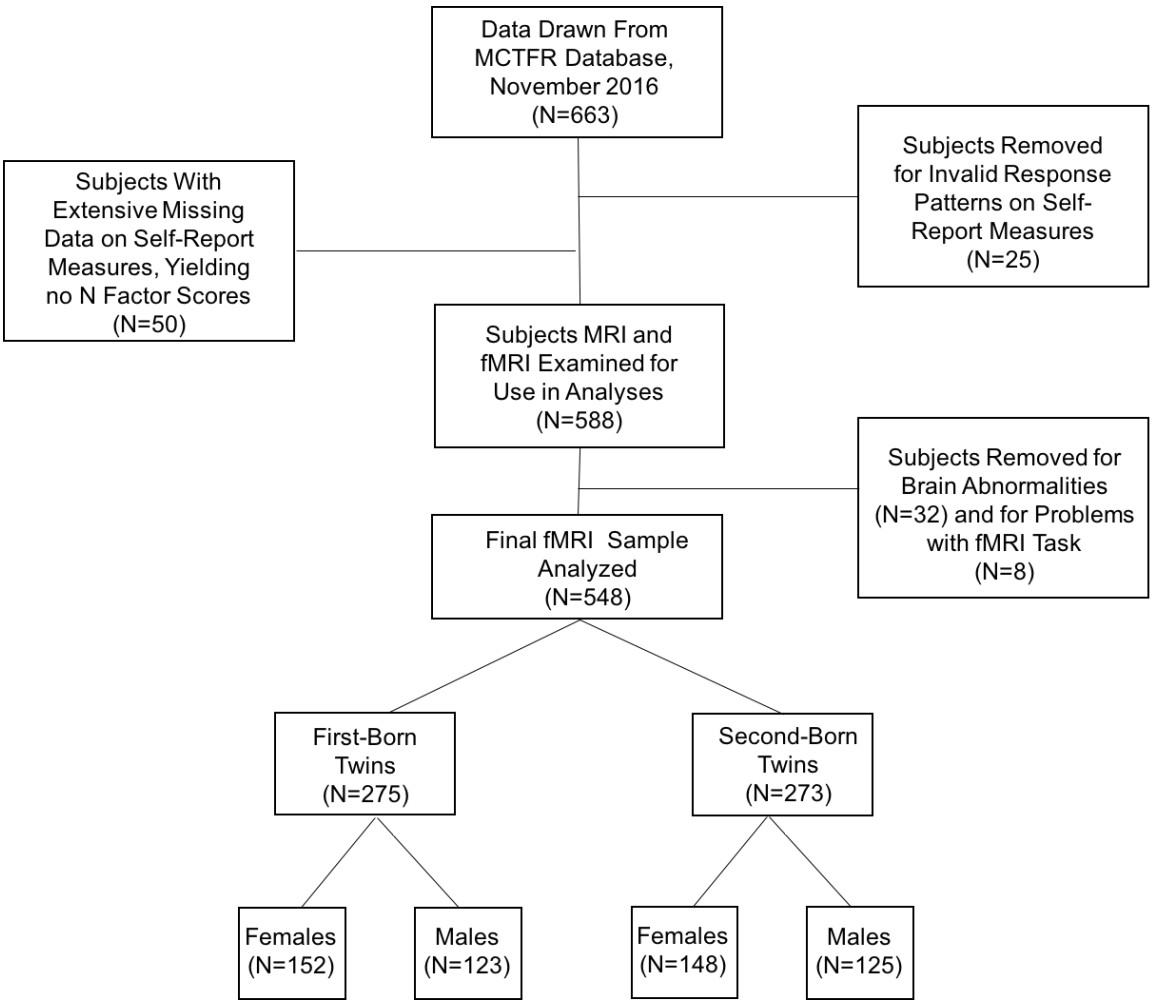

Figure 1. Consort Diagram.

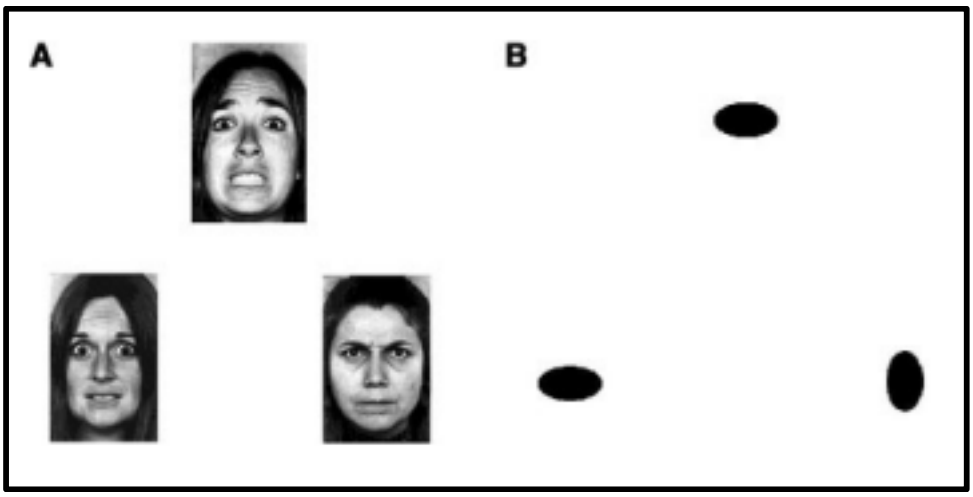

Figure 2. Experimental paradigm. Subjects performed this task while undergoing fMRI. In order to identify amygdala responses to facial expressions and to a neutral shape matching condition, subjects were asked to match one of two simultaneously presented images with an identical target image

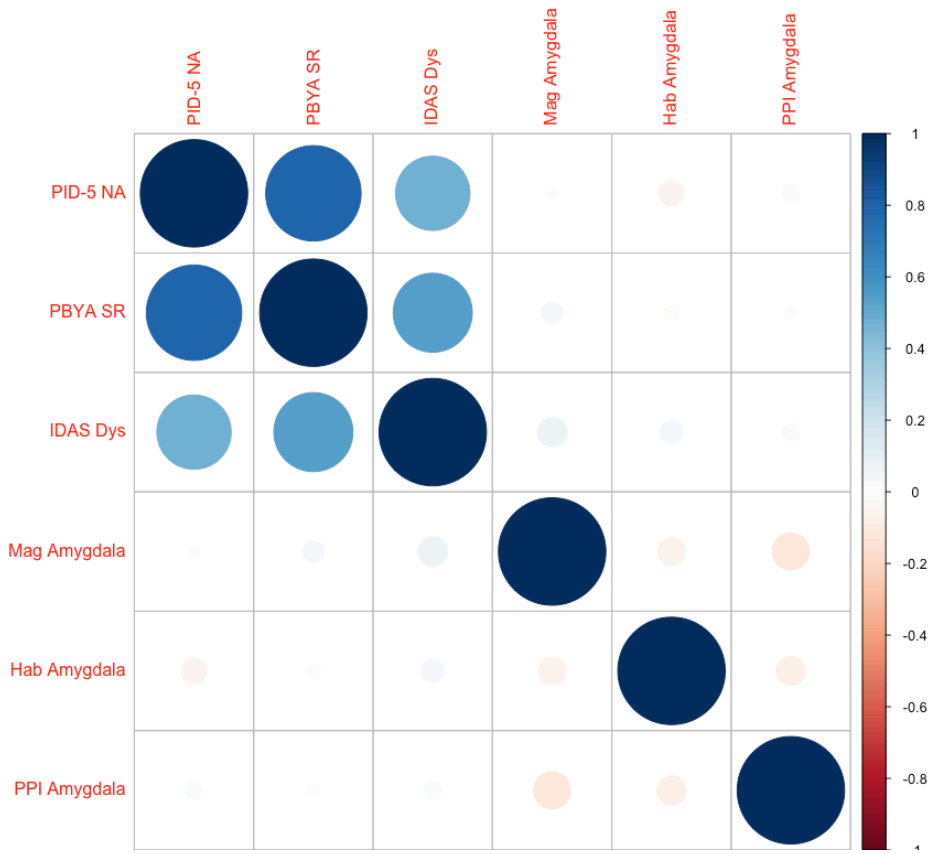

Figure 3. Intra- and Inter-Method Correlations. Results reveal moderate to strong correlations among the three self-report measures of neuroticism (PID-5 negative affect, PBYA stress reactivity, and IDAS-II dysphoria). Results reveal very weak correlations among the hypothesized neural markers of neuroticism. Inter-method correlations among the self-report measures and the hypothesized neural markers reveal very weak correlations across methods, suggesting that the neural markers may not be associated with self-reported neuroticism, at least as measured by these three scales.

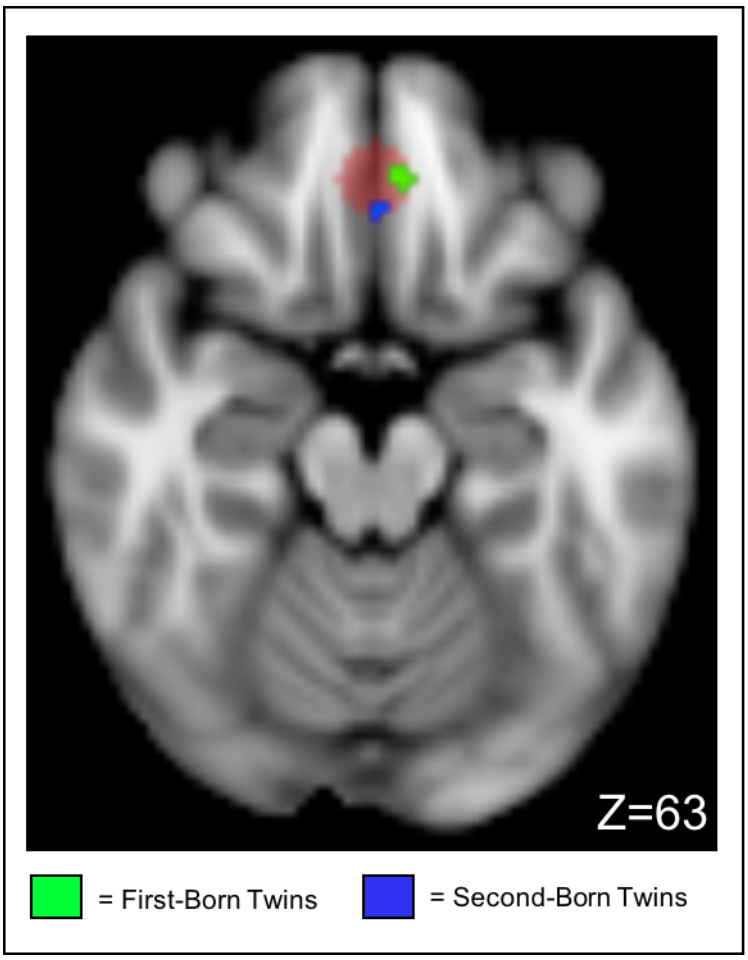

Figure 4. Amygdala-vmPFC Connectivity. In this figure, the red indicates the vmPFC region of interest based on the meta-analysis of emotion regulation (Diekhof et al., 2011). Overlaid are the regions of significant association between the amygdala and vmPFC in each of the twin groups. The small size of the significant regions provides one possible challenge for a psychoneurometric model of fMRI data – when the values are extracted from the entire theory-driven ROI (which in and of itself is not large), the non-significant voxels end up watering down the significant regions such that the relationship is no longer present. On the other hand, to extract values from these small regions would represent a case of "double-dipping" which would lead to inflated relationships (Vul, Harris, Winkielman, & Pashler, 2009; Vul & Pashler, 2012).

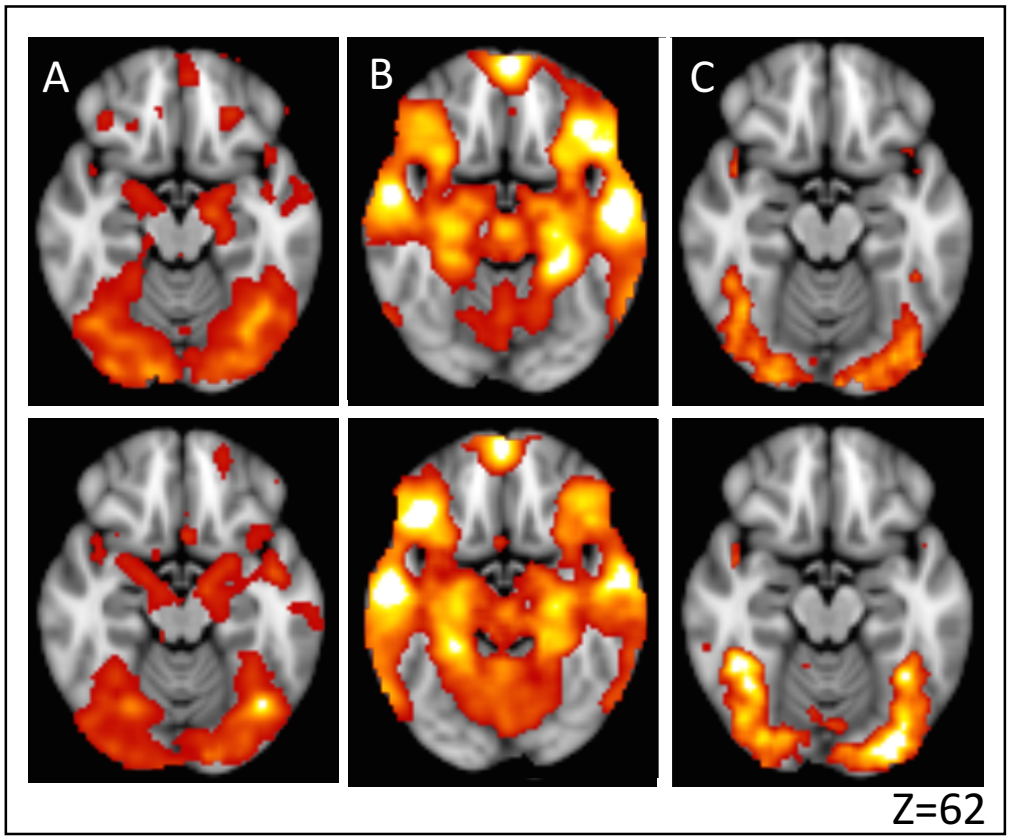

Figure 5. Whole-group Brain Activation Maps. Mean activation in first-born (top panel) and second-born (bottom panel) twins. Group activation at the $z > 2.3$ ($p < .05$) level for the first-born twins and the second-born twins from the A) magnitude of emotion>shape contrast, B) negative trend of habituation of emotion>shape contrast over the course of the task, and C) amygdala-whole brain connectivity during the emotion>shape contrast. The task reliably activates the amygdala in both twin groups and the results of the three task analyses map onto similar previous findings and theoretical patterns of activation from whole group analyses in the absence of covariates (aside from scanner type).

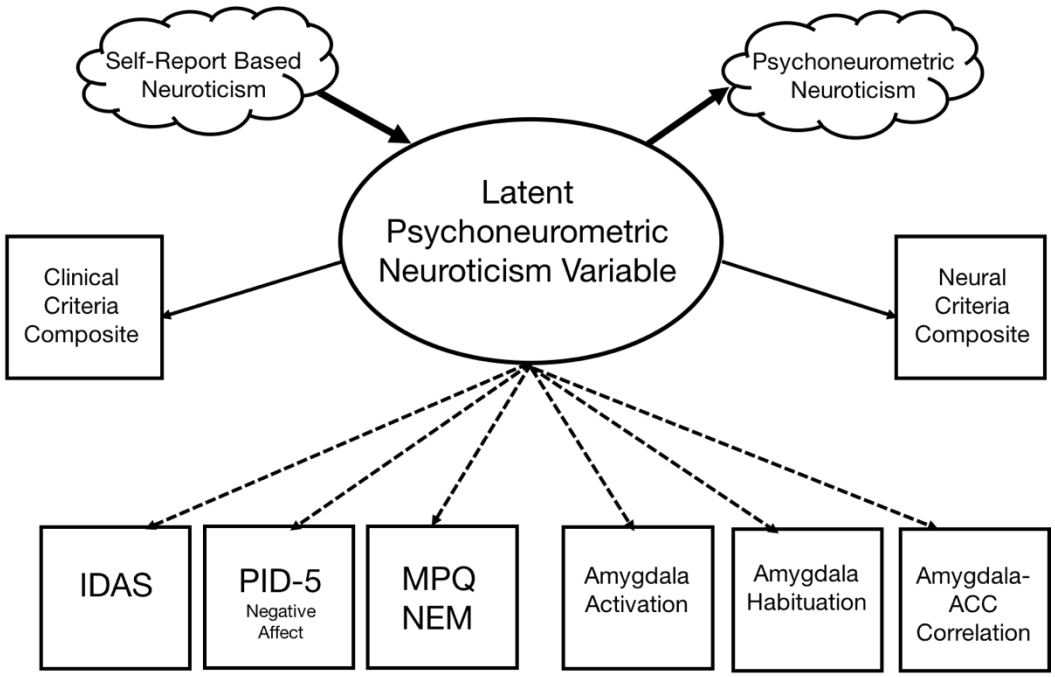

Figure 6a. Conceptual Psychoneurometric Model. This conceptual figure, modeled off of empirical findings using the psychoneurometric approach (Yancey et al., 2016), diagrams the goals of such a methodology. The bottom of the figure depicts the psychological and neural indicators. These indicators will be factor analyzed to determine their loadings onto a latent psychoneurometrically derived neuroticism score. By using this process, the hope is to be able to update the construct of trait neuroticism from one derived purely by using self-report, to one derived by using multiple-methods across more than one measurement domain. As Yancey and colleagues highlight, this type of methodology supports Chronbach and Meehl's (1955) notion of 'bootstrapping,' using multiple related measures in order to improve construct validity.

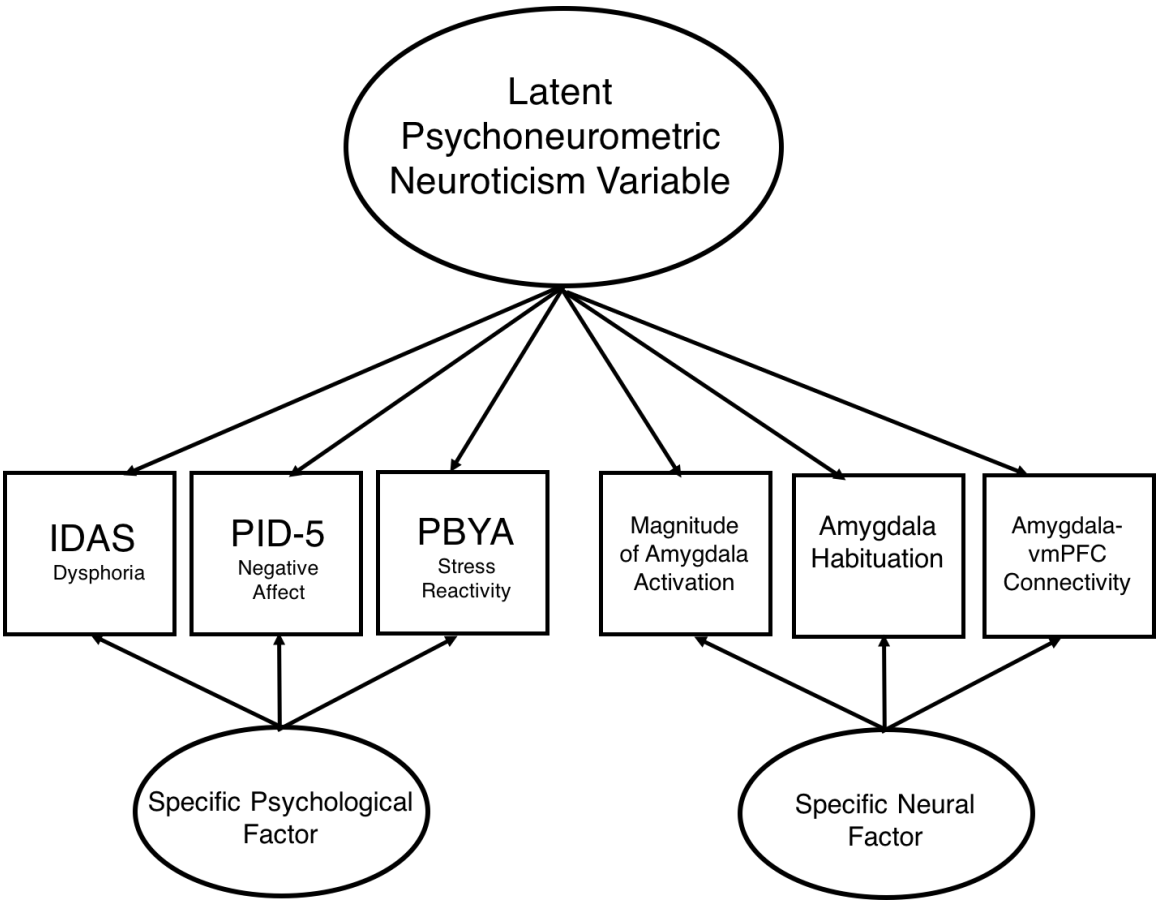

Figure 6b. Hypothesized Bifactor Model. If this model best characterized the data, there would emerge a general psychoneurometric neuroticism factor that would saturate all of the scales. The specific self-report measure scales and neuroscientifically-derived markers, though, would be saturated with the general psychoneurometic neuroticism factor, as well as the measurement domain factors (e.g., psychological scales would be saturated with psychological factor, neuroscientifically-derived markers would be saturated with the neural factor). These two measurement-specific factors would not be correlated with one another. This model would indicate that the model is saturated by the broad psychoneurometric model, but that the specific scales and markers are saturated by their measurement specific factors, which vary independently of the general factor. Because the association among the hypothesized neural markers and between

hypothesized neural markers and the self-report measures did not emerge, this model did not accurately characterize the data in this sample. The Schmid-Leiman transformation (Schmid & Leiman, 1957) is used to transform an oblique factor solution containing a hierarchical factor solution into an orthogonal solution, such that there are independent loadings of variables on factors at varying levels of the model.

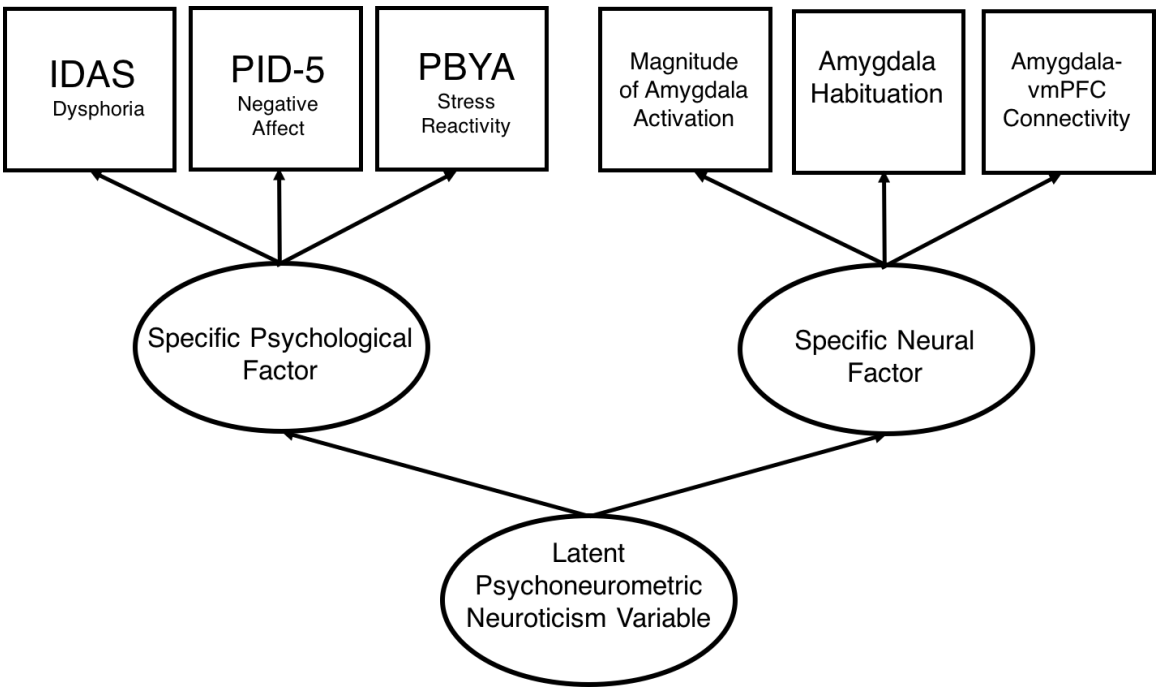

Figure 6b. Hypothesized Higher-Order Model. If this model best characterized the data, there would emerge a general psychoneurometric neuroticism factor. This factor would bifurcate into distinguishable factors (psychological neuroticism and neuroscientifically-derived neuroticism) that would then be further sub-divided into the specific self-report scales and neural markers. In this model, the correlations among the scales would be accounted for by the two higher-order sub-factors (psychological and neuroscientifically-derived neuroticism) and the relationship between the sub-factors would be explained by the overarching factor. Because the association among the hypothesized neural markers and between hypothesized neural markers and the self-report measures did not emerge, this model did not accurately characterize the data in this sample.

Appendix A. R Code for Psychoneurometric Modeling

```
# packages that come in use
library(psych)
library(MASS)
library(GPArotation)
library(lavaan)

# read table from desktop
data <- read.csv(file="/Users/Merav/Google
Drive/Dissertation/FSL_Data/Featquery_AmygdalaMarkers_050817.csv",head=
TRUE,sep=",")

# set -99 to be N/A (i.e., missing values)
data[data==-99] <- NA

#### see structure/variable names/other descriptives of data
# check number of rows and columns
colnames(data)
dim(data)
# make sure first few people and last few people look fine
headTail(data)
# descriptive statistics
describe(data)

#####################################################

#### SINGLE-LEVEL MODELING ####

# One-level factor analyses of each measurement domain to later
correlate with factor scores for psychoneurometric models

# select psychological scales to include in the model
psych1 <- data[,c(6,10,13)]
# make correlation matrix
psych1.cor <- cor(psych1, use="pairwise")
# do 1-factor factor analysis --> make sure fit is okay
psych1.fa <- fa(psych1.cor)
# estimates number of factors and principal components
fa.parallel(psych1)
# extract factor scores
psych1.scores <- factor.scores(psych1, psych1.fa$loadings)$scores


# select neural scales to include in the model
neuro1 <- data[,c(22,23,26)]
# make correlation matrix
neuro1.cor <- cor(neuro1, use="pairwise")
# do 1-factor factor analysis --> make sure fit is okay
neuro1.fa <- fa(neuro1.cor)
# estimates number of factors and principal components
fa.parallel(neuro1)
# extract factor scores
neuro1.scores <- factor.scores(neuro1, neuro1.fa$loadings)$scores


# other factor analysis methods for neural variables
# maximum likelihood factor analysis
neuro1.fa <- fa(neuro1.cor, fa="ml")
# principal axis factor analysis
neuro1.fa <- fa(neuro1.cor, fa="pa")

#####################################################
```

```
#### Bifactor ####

# 3-factor factor analysis w/ bifactor rotation
bf.mod1 <- fa(model1.cor, 3, rotate="bifactor")
# print all loadings (cross loadings should be close to 0)
print(bf.mod1$loadings, cutoff=0)


#####################################################

#### Bifactor w/ Schmid-Lieman Transformation ####

# 2 factors for 2 residual method factors
sl.model <- schmid(model1.cor, nfactors=2)
# correlation between factors
sl.model$phi
# loading of lower order factors onto higher order factor
sl.model$gload
# loading matrix
sl.model$sl
# loadings on gen factor (row=# vars in model, col=1 factor)
gen.loadings <- matrix(sl.model$sl[,1], nrow = 6, ncol = 1)

#fit stats (bottom provides fit statistics -> same as hierarchical)
sl.fit.model <- schmid(model1.cor, nfactors = 2, n.obs = N)
sl.fit.model

#####################################################

#### Higher-order Model ####

# diagram higher-order model
om.model1.h <- omega(model1, 2 ,sl=FALSE, digits=3, title="Model 1")
# output of higher-order (loadings)
om.model1.h

##the value "Omega Higher-order" from above object is the general
factor saturation i.e., the proportion of variance in all of the
variables accounted for by the general factor##

# run the higher-order model by hand to check loadings/ get factor
scores
# create 1-level general factor
fa1.m1 <- fa(model1, 1)
# extract general factor scores (or g.fa <- fa1.m1$scores)
g.fa <- factor.scores(model1, fa1.m1)$scores

# lower order factors (2 factors)
fa2.m1 <- fa(model1, 2)
# make sure variables load on right factor (eg. brain variables load
onto brain factor, psych variables load onto psych factor)
print(fa2.m1$loadings, cutoff=0)

# extract lower order factor scores
lowerorder.scores <- factor.scores(model1, fa2.m1, fa2.m1$Phi)$scores
psych.fa2 <- lowerorder.scores[,1]
phys.fa2 <- lowerorder.scores[,2]

# create general, higher-order factor
phi.fa2 <- fa2.m1$Phi
# correlations between lower order factors
round(phi.fa2, 2)
```

```
#factor loadings of lower order on higher order based on correlation
matrix above
h.fa <- fa(phi.fa2)
```