Associations Between Reward Processing in the Monetary Incentive Delay Task and Higher Order Factors of Psychopathology

By

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Chapter 1

Introduction

My aim in this thesis is to examine the relationship between neural responses to reward anticipation and reward attainment in the MID task and higher order psychopathology factors, as estimated using a bi-factor model. My aim is of an interdisciplinary nature, that lies at the intersection of neuroscience, clinical psychological science and quantitative psychology. For this reason, in this introductory section I will attempt to justify my aim and hypothesis by providing a review of the various literatures that are pertinent to my constructs of interest. I will begin by reviewing the history and literature of using dimensional factor analytic models to model psychopathology, including the bi-factor model approach used in this study (Section 1.1), and the neural correlates of these higher-order dimensional constructs (Section 1.2). Then, I will turn to the construct of reward, exploring theoretical models surrounding reward processes supporting a distinction between reward anticipation and attainment stages (Section 1.3), as well as the neural circuits involved in these reward processes (Section 1.4). Finally, I will review current literature linking neural differences in reward processing and psychopathology, and articulate my hypothesis (Section 1.5).

1.1 Dimensional conceptualizations of psychopathology: introducing the bi-factor model

One of the most debated questions in the field of psychopathology has revolved around the question of nosology. How exactly should psychopathology be understood, measured, classified and organized? This is a central question that affects a wide array of stakeholders, whether it is clinicians trying to conceptualize a case and develop a treatment plan, researchers attempting to narrow down constructs and test hypotheses to advance clinical psychological science, or even patients who are attempting to have a better understanding

of what is going on with them and how it affects who they are.

Currently, the prevailing nosologies in clinical and research work are those espoused by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and the *International Statistical Classification of Diseases and Related Health Problems* (ICD), which have been referred to as the DSM-ICD nosologies. The DSM-ICD nosologies are underpinned by two important assumptions. First, almost all DSM-ICD disorders are understood as etiologically distinct, largely episodic, categorical entities, which are assumed to differ qualitatively from "normality" and from each other. Second, the DSM-ICD approach makes an assumption (usually referred to as neo-Kraeplinian) that disorders could be differentiated solely on the bases of signs (observable manifestations) and symptoms (patient reports) (Lilienfeld & Treadway, 2016).

The DSM-ICD nosology has provided some important benefits to the advancement of clinical practice and psychopathology research. By providing a well delineated "lingua franca" to facilitate communication of diagnostic information and measurement of these constructs, the DSM-ICD nosology has provided a good starting point for clinical measurement and studies of psychopathology. Some DSM-ICD categories have also shown consistent associations with family history and neural factors[1], which is one way of supporting their construct validity. Additionally, DSM-ICD categories allowed for the development of specifically targeted empirically supported treatments (e.g., Cognitive Behavior Therapy for Depression) (Lilienfeld & Treadway, 2016).

However, the DSM-ICD nosology has also faced some challenges. Perhaps one of the largest challenges to this approach is the very high observed co-morbidity across psychiatric disorders (Lilienfeld & Treadway, 2016). For the DSM-ICD assumption that disorders are etiologically distinct categorical entities that differ from one another, one might expect to find that these categories largely tend to be mutually exclusive, with little co-occurrence.

[1]For example, one large meta-analytic study found larger polygenic loadings for schizophrenia in cases with a greater family history of illness (Bigdeli et al., 2016); another meta-analysis found structural and functional alternations in patients with depression (Sacher et al., 2012).

Yet, epidemiological studies measuring psychopathology using the DSM-ICD approach have revealed very high rates of co-morbidity across several epidemiological studies, with a recurrent pattern that half of people with one disorder have met criteria for another disorder, and half of those met criteria for a third disorder, and so on (Newman, Moffitt, Caspi, & Silva, 1998). In the seminal U.S. National Co-morbidity Survey study, Kessler et al. (1994) found that 48% of those surveyed reported suffering one or more disorder in their lifetime; 27% experienced two or more disorders in their lifetime; and 14% experienced three or more disorders in their lifetime. Similarly, in the Netherlands Mental Health Survey and Incidence Study (NEMESIS), Bijl, Ravelli, and Van Zessen (1998) found that 41.2% of respondents experienced 1 or more disorder in their lifetime; 18.5% of respondents experienced two or more disorders in their lifetime; and 9.2% of respondents experienced three or more disorders in their lifetime. In the prospective Dunedin Multidisciplinary Health and Development Study cohort, 47.3% of participants who were diagnosed with any one psychiatric disorder were likely to be diagnosed with multiple disorders (Newman et al., 1996).

Developmentally, the counter-part to the phenomenon of co-morbidity is heterotypic continuity: the extent to which a disorder (A) can predict the incidence of a distinct disorder (B, C, etc.) later on in time. Several studies have shown that there is significant heterotypic continuity across the lifespan for DSM-ICD categories (Copeland, Shanahan, Costello, & Angold, 2009; Lahey, Zald, Hakes, Krueger, & Rathouz, 2014; Moffitt et al., 2007). For example, in one of these studies Lahey et al. (2014) assessed homotypic and heterotypic continuity between two waves separated by three years in the National Epidemiologic Study of Alcohol and Related Conditions (NESARC). Lahey and colleagues found statistically significant bi-variate associations for nearly all heterotypic continuities, with a median tetrachoric correlation of $\rho = .28$.

In the eyes of some authors, these recurrent empirical findings of heterotypic continuity and co-morbidity suggests that the DSM is not drawing the correct diagnostic boundaries

(e.g., Piccinelli (1998)). Other authors have taken this further, for example arguing that co-morbidity across disorders might illustrate the propensity of the DSM to attach different names to slightly different manifestations of a shared predisposition (Maj, 2005), an error known as the "jangle fallacy" (Block, 1995; Lilienfeld & Treadway, 2016).

Following on this vein, several authors began to use factor-analytic techniques to explore the possibility that there may be underlying, latent dispositions that would explain the high co-morbidity (or, statistically speaking, co-variance) across our current nosology of psychiatric disorders. This line of work can be traced as far back as the work of Achenbach (e.g., Achenbach and Edelbrock (1978)), who pioneered early efforts to use factor analysis of symptom reports to empirically derive dimensions of psychopathology. Since then, a wealth of evidence has emerged in support of the idea that the co-variance structure of psychopathology symptom dimensions can be replicated using dimensional factor-analytic models (Krueger, Caspi, Moffitt, & Silva, 1998; Vollebergh et al., 2001; Krueger, McGue, & Iacono, 2001; Walton, Ormel, & Krueger, 2011; Markon, 2010; Cosgrove et al., 2011; Wright et al., 2013; Lahey et al., 2012; Caspi et al., 2014). Furthermore, these higher-order dimensional models do not just fit the data well, they can outperform traditional categorical diagnoses in terms of both prognosis and stability (Krueger et al., 1998; Vollebergh et al., 2001; N. Eaton, Krueger, South, Simms, & Clark, 2011; N. R. Eaton et al., 2013), predicting treatment seeking (Sunderland & Slade, 2015), and assessing functional impairment (Markon, 2010; Sunderland & Slade, 2015).

A few important departures are observed in this new line of work from the DSM-ICD nosology. First, in these approaches DSM-ICD symptom dimensions are not assumed to be mutually exclusive, but rather they are all manifestations of higher-order dispositional factors[2]. Second, in these approaches the higher-order dispositional factors are specified

[2]It is important to note here that the extent to which these models are "theoretically independent" of the DSM-ICD organization of symptoms into categories varies across studies, depending on the psychopathology assessment instrument being used and the modeling approach being taken. For example, some studies specify models that use as manifest variables symptom counts for DSM-ICD dimensions; in this case, the authors are still are presuming symptoms should be aggregated into manifest variables that map onto DSM-ICD categories. Other models, e.g. those that use data from Achenbach's measurement instruments

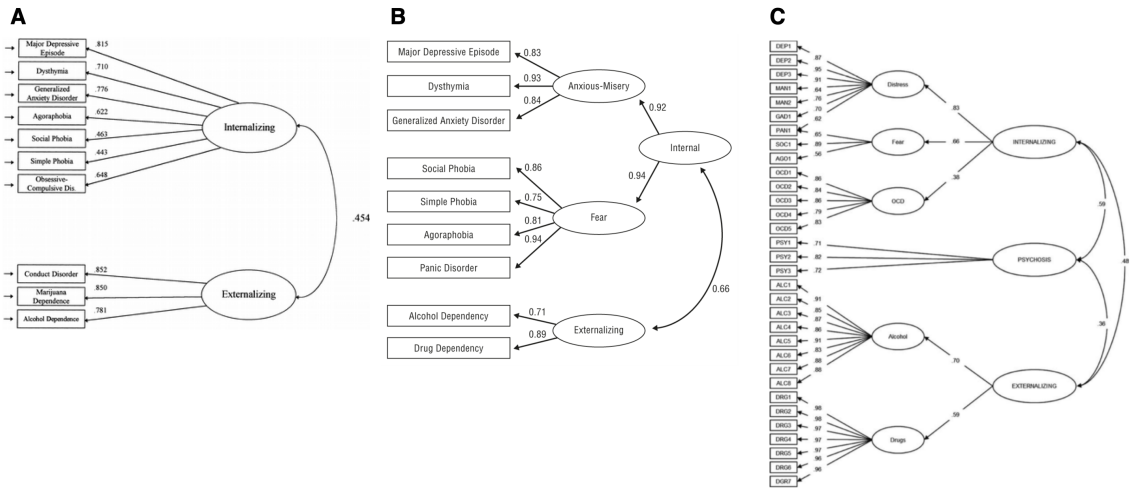

Figure 1.1: Three examples of dimensional CFA model specifications used to model psychopathology across the literature. Panel A is reproduced from Krueger et al. (1998), in which he used a two-factor orthogonal solution. Panel B is reproduced from Vollebergh et al. (2001), in which Anxious-Misery and Fear factors load onto a third-order Internalizing factor, which correlates with the Externalizing factor. Note also that Externalizing here does not include antisocial personality/conduct disorder. Panel C is reproduced from Wright et al. (2013), who break down Internalizing into Distress, Fear and OCD subfactors, and also include a third Psychosis factor that is oblique to the Internalizing and Externalizing factors.

as dimensional trait-like constructs, as opposed to categorical types[3]. Third, these trait-like constructs are modeled on the basis of longer time periods rather than present experience of symptoms (i.e., either lifetime or 12-month period). One advantage of this longer purview of time consideration in the higher-order factor analytic approach is that it provides a better account for heterotypic continuity, focusing less on specific presenting symptoms at a given point in time and more on broad domains of dysfunction that could underlie changing symptoms (Lahey et al., 2014).

like the CBCL, might instead presume that symptoms should be organized in accordance with the dimensional scales proposed by the instrument's manual, which may not necessarily map onto the DSM-ICD approach. Achenbach's instruments, for example, condense generalized anxiety and depression into one scale, the "anxious-depressed" scale, which does not map onto the distinction in DSM-ICD between anxiety disorders and depression. Thus, some approaches might therefore have "anxious-depressed" as a manifest-variable instead of separating these into "anxiety" and "depression". I articulate this point here to elucidate that these higher-order approaches are in most cases not entirely "DSM-ICD free" in their theoretical underpinnings.

[3]The performance of categorical, hybrid and dimensional approaches has been empirically compared and supports the use of dimensions as opposed to these alternative approaches; see Wright et al. (2013).

Although there is no formal strict consensus on the specific factor structure that should be used to model psychopathology data, most models in the literature today are variations or extensions from earlier designs in which two oblique factors (Externalizing and Internalizing) load onto symptom or diagnosis data (the spirit of this approach is synthesized well by Krueger and Markon (2006)). To illustrate, one such archetype is a study by Krueger et al. (1998), which specified an oblique two-factor solution: an externalizing factor that loaded onto alcohol dependence, marijuana dependence, and anti-social personality disorder / conduct disorder; and an internalizing factor that loaded onto major depressive episode, dysthymia, generalized anxiety disorder, agoraphobia, social phobia, simple phobia, and obsessive-compulsive disorder. Figure 1.1 illustrates this factor structure (Panel A), as well as two examples of derivative variations or extensions of this structure published more recently, e.g. re-organizing internalizing into a hierarchical structure (Panel B) and/or including a psychosis factor (Panel C).

In spite of the variability in model specifications, across most of these latent factor models one finds that the Internalizing and Externalizing higher-order dimensions are not orthogonal, and in fact show a very high and significant positive correlation. This observation led Lahey et al. (2012) to model psychopathology in the adult NESARC sample using a higher-order bi-factor model, wherein all disorders were able to load onto a general factor, as well as three specific orthogonal Externalizing, Distress and Fear factors (see Figure 1.2, Panel A)[4]. The bi-factor model fit the data well[5], but most importantly, the general bi-factor measured in the NESARC Wave 1 prospectively predicted future psychopathology and functioning assessed in NESARC Wave 2, over and above the variance accounted for

[4]In this case, the manifest variables were DSM-IV diagnoses in the past 12 months as measured by the Alcohol Use Disorder and Associated Disabilities Interview Schedule - DSM-IV version (AUDADIS-IV), which included major depression, dysthymia, social phobia, specific phobia, generalized anxiety disorder, agoraphobia/panic disorder, antisocial personality disorder, tobacco dependence, marijuana dependence, alcohol dependence and other drug dependence. It did not include assessment of psychotic disorders or OCD.

[5]Although the authors originally argued that the bi-factor model fit the data "better" than the three-factor solution on the basis of log-likelihood and BIC (Lahey et al., 2012), given more recent arguments that bi-factor models are known for a propensity to over-fit, as well as other technical considerations (e.g., Bonifay, Lane, and Reise (2017)), I will abstain here from paraphrasing said controversial claim. I will delve deeper into problems with the bi-factor approach later in Section 4.4 (Limitations).

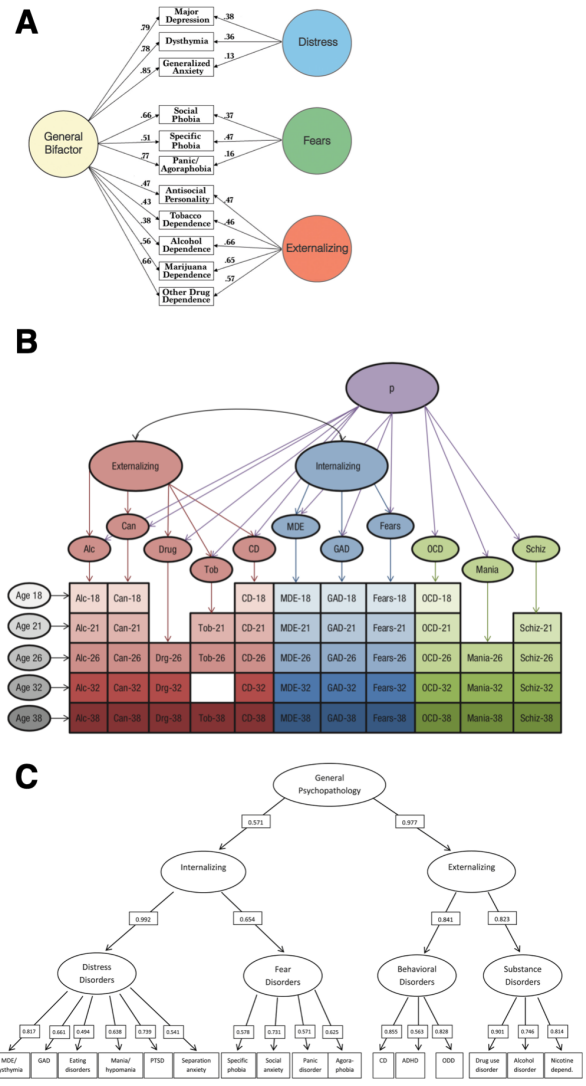

Figure 1.2: This figure illustrates three different examples of dimensional bi-factor CFA model specifications used to model psychopathology in the literature. Panel A, reproduced from Lahey et al. (2012), shows the first bi-factor model applied to psychopathology in the NESARC data set. Note how the internalizing and externalizing factors are orthogonal, as is standard practice for bi-factor models. Panel B, reproduced from Caspi et al. (2014), shows the bi-factor model variation specified by Caspi and colleagues. Note how the internalizing and externalizing residual factors are specified as oblique, and how "thought disorder" dimensions (i.e., schizophrenia, mania and OCD) are included. Panel C, reproduced from Blanco et al. (2015), illustrates a more sophisticated hierarchically-organized application of the bi-factor model to the NCS-A adolescent sample (as stated, this type of specification is a more restricted version of the type of bi-factor model specified in Panels A and B).

by the fears, distress, and externalizing factors (Lahey et al., 2012).

Another seminal study that popularized using the bi-factor approach to model psychopathology was that of Caspi et al. (2014), who applied this approach to model the structure of psychopathology of the Dunedin Study longitudinal dataset (from adolescence to midlife). Caspi and colleagues' study extended the original insights offered by Lahey et al. (2012) in several ways. First, Caspi and colleagues modeled psychopathology data longitudinally in a prospectively assessed representative sample. Second, Caspi and colleagues used symptom counts, as opposed to binary diagnoses, to estimate higher-order factors. Third, Caspi and colleagues included psychotic and thought-disorder dimensions in their model (i.e., OCD, mania and schizophrenia symptoms). Fourth, Caspi and colleagues allowed for a correlation between the residualized internalizing and externalizing factors, allowing them to examine whether (after controlling for the general factor) these factors still showed some sort of relationship between each other[6]. Finally, Caspi and colleagues were able to provide an initial nuanced assessment of the criterion validity of the general factor thanks to the rich phenotyping and wide array of measures collected in the Dunedin Study. The bi-factor model specified by Caspi and colleagues fit the data well (see 1.2 Panel B for an illustration of the model specification), and showed several associations of high clinical utility. For example, general psychopathology was more strongly correlated with family history of each disorder than were the specific factor scores[7]. Additionally, the general factor of psychopathology showed strong associations to several indicators of life impairment and brain integrity, as measured by IQ and Executive Function assessments. Caspi and colleagues branded the general factor as the *p*-factor, in an allusion to Spear-

[6]The authors were able to specify this correlation because the thought disorder factor was dropped and OCD / mania / schizophrenia symptom dimensions were allowed to load directly onto the general factor. Since these dimensions loaded onto the general factor without loading onto any residualized factor, the authors had enough general-factor specific variance to be able to estimate the correlation between the residualized internalizing and externalizing factors. Yet, while estimates converged in the overall data set, they did not converge in all the age sub-samples; for a more nuanced technical description of the limitations of this model specification and other concerns with the modeling approach taken by Caspi et al. (2014), see Markon (2018).

[7]With the exception of conduct disorder / anti-social personality and substance dependence, which were still highly correlated with residualized externalizing factor.

man's *g*-factor of intelligence.

Following the publication of these two studies, there has been a flurry of scientific studies testing the portability of the bi-factor approach to model psychopathology and the criterion validity of its higher-order latent constructs in different age ranges, populations, and modeling approaches[8]. Several studies found that the bi-factor model specification was able to fit psychopathology data for children well, and provided clinically valuable information. Pettersson, Lahey, Larsson, and Lichtenstein (2018) found a bi-factor model provided a good fit to item-level parental rating data from a structured interview administered as part of the Child and Adolescent Twin Study in Sweden (ages 9 & 12; $N = 16,806$). Additionally, Pettersson and colleagues found that the general factor of psychopathology estimated in childhood was predictive of significant higher odds of experiencing a wide array of adverse outcomes in adolescence, including anxiety diagnosis, depression diagnosis, anxiolytic and antidepressant medication use, alcohol abuse diagnosis, drug use diagnosis, conviction of crimes and ineligibility to begin high school, which supports the criterion validity of the general factor. In another study, Lahey et al. (2015) found that a bi-factor model fit mother-reports of symptoms[9] well in a sample of 5-11 girls ($N = 2,450$). Importantly, the general factor was robustly and independently associated with all measures of teacher-reported school functioning concurrently during childhood and prospectively during adolescence, yet again supporting the criterion validity of the general factor. Additionally, other studies have shown the bi-factor model fits adolescent data well. For example, Carragher et al. (2016) successfully fit a bi-factor model on a sample of 2,175 Australian adolescents aged 12-14 years from symptom-level endorsements[10]. In addition, other studies have been able to fit a more restricted version of the bi-factor model, in which the

[8]More specifically, whether the manifest variables used for model estimation are the presence or absence of symptoms, symptom counts across a dimension, or binary diagnoses.

[9]Higher order dimensions were modeled on the basis of symptom counts across dimensions assessed via two instruments. The Child Symptom Inventory-4 was used to assess inattention, hyperactivity-impulsivity, oppositional defiance, conduct disorder, and depression; while the Screen for Child Anxiety Related Emotional Disorders was used to assess generalized anxiety disorder, social phobia, separation anxiety disorder, school phobia and panic/somatic symptoms.

[10]The authors integrated items from several scales in this study

general factor model loads onto internalizing and externalizing factors, which in turn load onto symptom dimensions[11]. For example, Blanco et al. (2015) found that a hierarchically organized model provided an excellent fit to diagnosis data from the National Co-morbidity Survey Adolescent Supplement (NCS-A) (illustrated in Figure 1.2, Panel C).

Beyond the aforementioned evidence supporting the replicability and criterion validity of a general factor of psychopathology, there is also growing evidence suggesting that the general factor maps to some degree onto non-specific genetic risk factors. A massive study comprising almost 3.5 million participants from the Swedish National Registry (Pettersson, Larsson, & Lichtenstein, 2016) found that a general genetic factor influenced all disorders and convictions of violent crimes, accounting for between 10% (attention-deficit/hyperactivity disorder) to 36% (drug abuse) of the variance of psychiatric disorders. A more recent study by Selzam, Coleman, Caspi, Moffitt, and Plomin (2018) tested the hypothesis that there is a genetic general factor by estimating a genetic correlation matrix across psychiatric disorders using four different methods. Each of the principal component analyses corresponding to the four methods yielded a general factor on which all disorders loaded, explaining between 20% and 60% of the total variance. All in all, these studies appear to suggest that there exist genetic pleiotropic influences that increase risk for almost all psychiatric disorders, mapping onto the theoretical underpinnings of the general factor.

In their discussion, Caspi et al. (2014) argued that *p* may be a "'dimension that unites all disorders and has neurological roots." This sentiment was echoed by (Zald & Lahey, 2017), who argued that examining these higher-order psychopathology dimension phenotypes such as the general factor in using neuroimaging has the potential to reveal transdiagnostic neural substrates that non-specifically contribute to multiple forms of psychopathology. This study will attempt to address this call, by examining the neural correlates of higher-order psychopathology factors estimated using the bi-factor model approach.

[11] As indicated by Markon (2018), this type of model with a second-order general factor presume internalizing and externalizing mediate the relationship between the general factor and symptom expression, and they are mathematically nested within the bi-factor models I have been discussing.

1.2 Neural correlates of higher-order psychopathology factors

Because the idea of modeling psychopathology using a general factor is still relatively recent, the literature of studies looking at neural correlates of higher-order psychopathology factors is rather small. Additionally, one limitation in the existing literature is that it is primarily focused on children, adolescents and young adults. Still, here I will aim to provide a short survey of the existing body of research on this matter.

1.2.1 Structural correlates

Although not directly testing associations between the general factor of psychopathology and brain structure, in a meta-analysis Goodkind et al. (2015) evidenced that there are common structural abnormalities across psychiatric disorders. In this study, the authors here conducted a voxel-based morphometry meta-analysis of 193 studies comprising 15,892 individuals across 6 diagnostic groups (schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder and anxiety). The authors found that grey matter loss converged across diagnoses in three regions: the dorsal anterior cingulate (dACC), the right insula, and the left insula[12]. In a follow-up analysis of three independent healthy participant datasets, the authors then found that these common gray matter loss regions were interconnected into a network: these regions showed significant co-activation in tasks, and functional connectivity amongst each other at rest. Furthermore, lower grey matter in this network was associated with poor executive functioning (Goodkind et al., 2015). It is important to note here that this study did not explicitly model a higher-order bi-factor model, but rather, the authors aggregated several case-controlled studies and compared patient to non-patient (control) groups across disorders. So, while it would be improper to claim from this study alone that these regions are neural substrates of the general factor, these findings do show that reduced grey matter in these regions is associated with several major

[12]The authors reported that there were few diagnosis-specific effects, with only schizophrenia and depression being distinguishable from other diagnoses.

psychiatric disorders.

Snyder, Hankin, Sandman, Head, and Davis (2017) followed up with a study in which they attempted to directly identify associations between gray matter volume and higher-order psychopathology dimensions (from the bi-factor model). In this study, Snyder and colleagues leveraged a community sample of 254 children ages 6 to 10 and fit a bi-factor model onto parental reports scales from the Child Behavior Checklist (CBCL) and the Children's Behavior Questionnaire (CBQ). They found that the general factor of psychopathology was associated with reduced grey matter in the dorsal pre-frontal cortex (dPFC), the ventro-lateral prefrontal cortex (vlPFC), and the orbitofrontal cortex (OFC); while the internalizing factor was associated with reduced grey matter in the medial temporal lobe (MTL), the amygdala and the insula (no brain regions analyzed were associated with the externalizing factor) (Snyder et al., 2017)[13].

In a similar vein, Romer et al. (2018) also attempted to directly identify associations between gray matter volume and higher-order psychopathology dimensions (from the bi-factor model), although in this case with college-aged youth. Romer and colleagues found that higher general factor scores were associated with reduced grey matter volume in the occipital lobe and left cerebellar lobule VIIb (which is functionally connected with pre-frontal regions supporting cognitive control). Additionally, Romer and colleagues looked at the structural integrity of white matter pathways, and they found that higher general factor scores were associated with lower fractional anisotropy values[14] uniquely in the pons. Consistent with the large number of cerebellar afferents in the pons, Romer and colleagues also observed a significant positive correlation between the white matter integrity of the pons and cerebellar grey matter volumes associated with higher general factor scores. The authors interpreted their findings by positing that alterations in the structure of cortico-cerebellar circuitry supporting integration, coordination and monitoring of in-

[13] It is important to note as well that here, the authors selected only eight brain regions to analyze *a priori*; i.e., this was not a whole-brain analysis.

[14] Functional anisotropy, or FA, refers to the extent to which diffusion is restricted or unrestricted.

formation might be a contributing factor to general disposition to experiencing psychiatric symptoms.

1.2.2 Functional correlates

Taking a more developmental perspective, Sato et al. (2016) hypothesized that the maturation status of the default mode network (DMN) would be negatively associated with the general psychopathology factor. To test this, they recruited 654 students from schools in Brazil (ages 6 to 15) and assessed the extent to which the general factor of psychopathology was associated with default mode network (DMN) maturation (assessed here by looking at deviations of observed fALFF fluctuations in DMN regions of interest from those expected for the participant's age)[15]. The authors found that delayed individuals with delayed DMN maturation had significantly higher general factor scores than individuals with precocious DMN development, after controlling for age, gender and acquisition site. There were no differences in internalizing or externalizing factors associated with DMN development classification.

Additional compelling evidence for the functional correlates of higher-order factors comes from studies of the Philadelphia Neurodevelopmental Cohort (PNC). In one study, Shanmugan et al. (2016) examined whether higher-order psychopathology dimensions in youth were associated with executive system deficits using a working memory paradigm. They modeled psychopathology symptom endorsement from the GOASSESS interview using a bi-factor model, where they specified specified a general psychopathology factor and four orthogonal residualized dimensions of anxious-misery, psychosis, behavioral problems, and fear. Subsequently, the authors used multivariate and uni-variate approaches to test whether factor score estimates for higher-order symptom dimensions were associated

[15]Machine-learning techniques were used to predict the chronological age of subjects based on the fractional amplitude of low frequency fluctuations (fALFF) of regions of interest belonging to the DMN; then, a "maturational status" was defined for each subject based on the difference between the predicted and actual age of the participants. Consistent with previous studies, fALFF for the DMN was found to significantly predict the age of participants. (Sato et al., 2016)

with differences in the 2-back $>$ 0-back contrast in an *n*-back task[16]. The authors used multivariate pattern analyses were used to test for global effects, which revealed that general psychopathology was associated with a significant disturbance in global executive system recruitment; no other symptom dimensions showed a significant relationship for multivariate analyses. The authors then used uni-variate voxel-wise whole-brain analyses were to localize brain regions in which these associations were strongest, and to identify whether residualized factors might also show any regionally specific associations. Higher general psychopathology factor score estimates were associated with diminished activation of left and right frontal pole, anterior cingulate cortex, anterior insula, thalamus, and precuneus. Higher behavioral problems factor score estimates were associated with diminished activation of frontoparietal cortex, thalamus and cerebellum. Higher psychosis factor score estimates were associated with diminished activation in the left dorsolateral prefrontal cortex. Higher fear factor score estimates were marginally associated with diminished activation in medial frontal cortex, although this effect did not survive when re-doing the analysis excluding participants with poor performance in the 2-back condition. Finally, unlike the other dimensions, higher anxious-misery factor score estimates were associated with *increased* activation of multiple executive network brain regions including the anterior cingulate cortex, dorsolateral prefrontal cortex, parietal cortex, and thalamus.

In another study on the PNC sample, Kaczkurkin et al. (2017) conducted a whole-brain analysis to test the hypothesis that increased higher-order psychopathology dimension scores might be associated with differences in regional cerebral blood flow (rCBF) at rest. rCBF is a measure tightly coupled with regional brain metabolism at rest. Kaczkurkin and colleagues found that general psychopathology factor score estimates were associated with elevated perfusion in the right dorsal ACC and the left rostral ACC (worth noting, these were a small effects, with $r = .13$ for both). Looking at the residualized factors, the

[16] As a manipulation check to ensure the task was working, the authors also checked whether this contrast robustly recruited the executive network and resulted in deactivation of non-executive regions, which it indeed did.

authors found that the residualized psychosis factor was negatively associated with rCBF to the left frontal operculum / left insula ($r = -.11$), and the residualized fear factor was associated with decreased rCBF to the left subgenual ACC and the right occipital / fusiform gyrus ($r = -.14$ for both). One might note that in this study, higher general psychopathology factor scores were associated with increased perfusion to the ACC at rest, while in the aforementioned study by Shanmugan et al. (2016) (which was conducted on the same sample, using the same factor analytic model and dimensions) higher general psychopathology factor score estimates were associated with decreased engagement activation of the ACC in the *n*-back task contrast (which compared the harder to the easier condition). However, it is important to remember here that rCBF is measuring metabolism at rest, which is not necessarily the same as a measure of blood flow to this region during an executive function task, especially considering that the ACC plays a role in both emotional and cognitive processing[17].

1.3 Reward processing

Given the broad and dispositional nature of higher-order factors of psychopathology, it has been suggested that these higher-order factors may be associated with alterations in transdiagnostically-relevant psychological processes (Lahey, Krueger, Rathouz, Waldman, & Zald, 2017). One such possible mechanism is reward processing: indeed, as it will be discussed further on (see Section 1.5), abnormal reward processing is a prominent transdiagnostic feature of psychopathology (Zald & Treadway, 2017). Following, I will turn to a focused review of the literature on reward processes and their neural substrates.

Although there is still some debate pertaining to the precise taxonomy of reward processes, most current taxonomies draw from Robinson and Berridge's theoretical framework. Coming from the addiction studies literature, initially Robinson and Berridge offered

[17] I am thankful here to Dr. Kaczkurkin for responding to my email inquiry and explaining this valuable clarification to me.

the insight of distinguishing between two broad domains of reward processes. These are reward attainment (corresponding to "liking" the reward; e.g., the hedonic component) and reward anticipation (corresponding to "wanting" the reward) (Robinson & Berridge, 1993; Berridge & Robinson, 1998, 2003; Berridge, Robinson, & Aldridge, 2009). Following their initial publications, Robinson and Berridge updated their theoretical model to include a third "learning" component as well, which is tied to how cognitive and implicit learning can change the predictive value of a rewarding stimulus (Berridge & Robinson, 2003; Berridge et al., 2009)[18]. These distinctions found support across multiple levels of analysis, including neurophysiology, behavior and subjective reports (Berridge & Robinson, 2003; Berridge et al., 2009; Zald & Treadway, 2017).

Reward attainment is traditionally understood as the conscious, subjective experience tied to the evaluation or consumption of the rewarding object or event. In this conceptualization, one might for example measure and characterize this hedonic experience in an affective space through the dimension of valence, with positive valence reflecting increased hedonic value and negative valence reflecting an aversive experience (Russell, 2003; Zald & Treadway, 2017). Some authors have also hypothesized that there may also be some unconscious aspects to reward attainment, based on evidence showing that participants may alter their behavior after delivery of a "pleasurable" stimulus or drug even if they are not consciously aware they attained this reward (Berridge & Kringelbach, 2008)[19].

Reward anticipation can be broadly understood as a complex subjective, behavioral and neurophysiological state preceding and attuned to potential reward attainment. Subjectively, reward anticipation can be thought of as both "wanting" (in a more addiction-

[18]This domain will not be discussed at length here as it is not pertinent to the study at hand.

[19]For example, Winkielman, Berridge, and Wilbarger (2005) found that subliminal smiles did not cause any self-reported changes in mood or arousal, but it did cause thirsty participants to pour and consume more beverage, and increased their willingness to pay and their wanting of more beverage. Another piece of evidence commonly cited in support of this hypothesis comes from human psychopharmacology studies, in which participants were found to work more to receive a drug reward when they have been given a small dose of the drug vs. no drug at all, even if participants are unaware they received drug (i.e., the small dose produces no subjective effects or autonomic reactions) (Lamb et al., 1991; Hart, Ward, Haney, Foltin, & Fischman, 2001; Berridge & Kringelbach, 2008).

oriented sense, e.g., urges and cravings) and as an excitement or tension. Behaviorally, reward anticipation is mainly observed as approach behavior directed towards acquisition or goal attainment. Neuropsychologically, it is important to note that reward anticipation can sometimes (but not always) involve what Zald and Treadway (2017) have termed "reward facilitation": the facilitation of multiple perceptual, attentional, cognitive, and motor processes when rewards are at stake. Indeed, as Zald and Treadway (2017) have pointed out, the term "reward anticipation" is often used by researchers to describe the engagement and facilitation of all these processes (i.e., reward facilitation) rather than the explicit anticipation of a reward. This is the case for this thesis: when I refer to the "reward anticipation" stage of the Monetary Incentive Delay (MID) task (Knutson, Adams, Fong, & Hommer, 2001), I am referring to BOLD signal changes related to preparing to make a response to potentially gain a reward, rather than simply BOLD signal changes in expectation that a reward is about to be obtained.

1.4 Neural substrates of reward processing

A substantial body of neuroscientific work has identified a set of brain regions implicated in reward processing, as well as the anatomical connections between them; these are commonly referred to as "the reward circuit" or the "mesolimbic reward circuit". Figure 1.3 illustrates the structures and anatomical pathways in the reward circuit, which are embedded within a cortico-striatal loop and efferents that modulate the functioning of that loop. The reward circuit comprises the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), the ventromedial prefrontal cortex (vmPFC), the ventral striatum (VS), the ventral pallidum (VP), and the dorsomedial thalamus and midbrain dopamine neurons. Broadly, the circuit is formed as VS receives cortical inputs from ACC, vmPFC and OFC and then relays its outputs to VP, which subsequently projects information back to cortex via thalamus (Haber & Knutson, 2010).

Given the importance of sensory information to reward processing, it is also worth

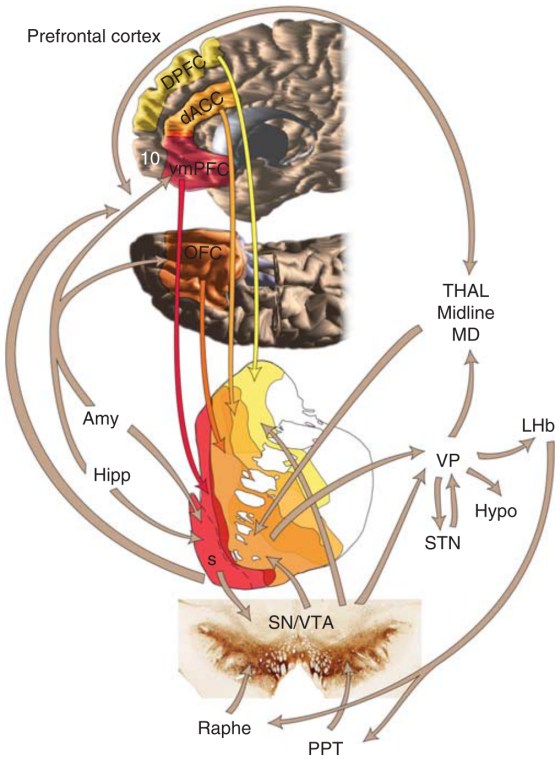

Figure 1.3: Schematic illustrating key structures and pathways of the reward circuit. Reproduced from Haber and Knutson (2010).

mentioning that while reward circuit does not receive any direct sensory input, it does receive processed sensory information. For example, the VS receives its primary input from OFC, ACC, and insula; these three areas integrate sensory information from across the senses, particularly OFC and insula. The VS also receives input from the amygdala, which is also strongly associated with sensory processing (Haber, 2011).

It is also important to keep in mind that the reward circuit also interacts with other cortico-basal ganglia circuitry. Although initially it was believed that the reward (a.k.a. "limbic") circuit functioned in parallel and in isolation from other cortico-basal ganglia circuits like the associative (a.k.a. "cognitive" or "prefrontal") circuit and the motor circuit (Alexander, Crutcher, & DeLong, 1991), more recent evidence has shown that there are integrative mechanisms in the brain through which information can be transferred between these circuits (e.g., Draganski et al. (2008); Haber, Kim, Mailly, and Calzavara (2006)). This suggests that the cortico-basal ganglia circuitry is capable of both parallel and integrative processing, which in turn implies that the reward circuit does not work in isolation (Haber & Knutson, 2010). This is consistent with the complexity of reward processing, which itself requires integration of multiple different sources of information. Indeed, to predict and evaluate a reward's value, and leverage that data to come up with and execute a planned behavior, the brain needs to: (1) combine incoming sensory information with reward value, expectation, and memory for past outcomes of actions and events; (2) integrate that information with cognition to develop a plan; and (3) relay this plan to motor control, which will execute the planned response or behavior (Haber, 2011).

Human neuroimaging studies of reward have sought to measure changes in neuronal activity due to reward processes. A multitude of different tasks and paradigms have been used in this literature, differing in the nature of the reward (e.g., monetary, erotic, food, social) (Knutson, Westdorp, Kaiser, & Hommer, 2000; Barrós-Loscertales et al., 2010; Felsted, Ren, Chouinard-Decorte, & Small, 2010; Izuma, Saito, & Sadato, 2008) as well as the degree and type of involvement required of the participant. Although there is evidence

showing that these factors do, indeed, lead to some degree of variability in the spatial distribution of neural response (c.f. Sescousse, Caldú, Segura, and Dreher (2013)), meta-analytic findings aggregating across these different paradigms have found some convergence consistent with the functional recruitment of the reward circuit in reward processes.

To assess whether human functional neuroimaging paradigms are able to engage the reward network, X. Liu, Hairston, Schrier, and Fan (2011) conducted a meta-analysis in which they organized peak activation foci from 142 studies by valence (positive or negative)[20] and processing stage (reward anticipation or reward attainment)[21], and then used two competing algorithms (Activation Likelihood Estimation, or ALE, and Parametric Voxel-Based Meta-Analysis, or PVM) to identify brain regions that showed robust engagement during reward processing. When looking at overall effects across valence and processing stage, both ALE and PVM algorithms identified significant engagement of almost all of the key reward circuit regions mentioned above that can be reliably surveyed using neuroimaging approaches: VS[22], medial and lateral OFC, and ACC; as well as significant associations with other regions postulated to regulate the reward network, including the amygdala (ALE only, n.s. for PVM), the dorsolateral and dorsomedial prefrontal cortex (dlPFC / dmPFC), the anterior insula, and the inferior parietal lobule (X. Liu et al., 2011).

The meta-analysis referenced above also found differences in which brain regions reward anticipation and reward delivery tend to engage, lending additional support to the taxonomical distinction between reward anticipation and attainment as well as the ability of

[20]Specifically pertinent to this manuscript, the "positive valence" category of studies included anticipation or attainment of: winning money or points, winning the larger of two sums of money or points, losing the smaller sum of money or points, receiving encouraging words in the screen, receiving a sweet taste in their mouths, and any other types of positive rewards as a result of successful completion of the task. Although not discussed due to not being too pertinent to the study at hand, the "negative valence" category included those in which participants lost money or points, did not win money or points, won the smaller of two sums of money or points, etc. (X. Liu et al., 2011).

[21]The authors defined reward anticipation as "the time period when the subject was pondering potential options before making a decision", while reward attainment was defined as "the period when the subject received feedback on the chosen option" (X. Liu et al., 2011).

[22]It is important to note here that the authors did not mention the Ventral Palladium in their results interpretation for overall effects. It is likely that the VP was still significant, but "swallowed in" to the massive basal ganglia cluster the authors are referring to as VS. This distinction or clarification was not made in the paper, but it is consistent with the activation maps show in Figure 2 of the paper.

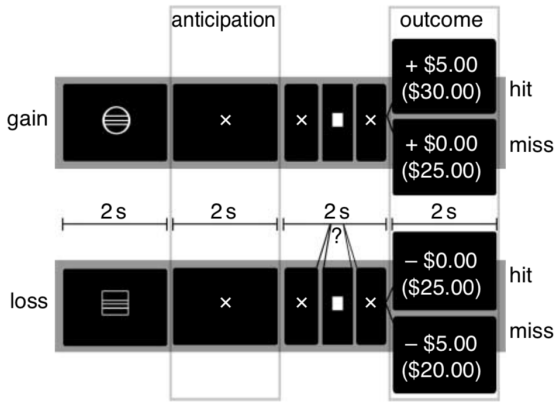

Figure 1.4: Prototypical MID task gain and loss structure; reproduced from Knutson and Greer (2008)

neuroimaging paradigms to differentiate spatio-temporal responses corresponding to these two processes. Reward anticipation showed more consistent engagement of the bilateral anterior insula, ACC/SMA, inferior parietal lobule and brainstem than reward attainment. Conversely, reward attainment preferentially activated ventral striatum, medial OFC, and amygdala relative to the anticipation phase. These differences in brain region recruitment are consistent with the distinction between reward anticipation and attainment (X. Liu et al., 2011).

As suggested by this meta-analysis, fMRI paradigms allow us to probe engagement of reward circuitry in humans. These types of paradigms allow for measurement of individual differences across individuals in this circuit, and have increasingly been used to prove the neural substrates of reward dysfunction in psychopathology and temperament (Zald & Treadway, 2017). In the following sub-section, I will focus my review to discuss more in depth one of the most popular human fMRI paradigms out there, the Monetary Incentive Delay (MID) task paradigm (Knutson et al., 2000), which is used in this study.

1.4.1 The Monetary Incentive Delay (MID) task paradigm

First introduced by Knutson et al. (2000), the MID task is a cued response task whose design was inspired by the work of Wolfram Schultz (Schultz, 1998; Knutson & Greer, 2008). The typical organization of a prototypical MID task is illustrated in Figure 1.4. Participants initially see a cue representing that they will have will have the chance to either gain or avoid losing a certain amount of money, followed by a fixation cross. Then, a target briefly appears on the screen (180-280ms), and participants have to try to press a button before the target is replaced by a fixation cross again. Lastly, participants see the outcome of their performance on that trial and cumulative earnings in the task.

The MID task has been shown to robustly engage core elements of the reward circuit. In the first neuroimaging study using the MID (in which anticipation and attainment were modeled together) the reward condition showed increased engagement of bilateral insula, nucleus accumbens, caudate, putamen, medial PFC, and supplementary motor area (SMA) / motor cortex (Knutson et al., 2000). In a follow-up study, in which anticipation and outcome phases were modeled separately[23], the reward anticipation phase showed increased engagement of bilateral insula, bilateral nucleus accumbens, bilateral caudate, left putamen, thalamus, right amygdala, medial prefrontal cortex, supplementary motor area, left motor cortex and cerebellar vermis; while the reward outcome phase tended to engage the right caudate, right putamen, thalamus, orbitofrontal cortex, anterior cingulate, posterior cingulate, and parietal cortex (Knutson, Fong, Adams, Varner, & Hommer, 2001).[24]

Indeed, another strength of the MID task is that it has allowed researchers to compare how different areas in the reward network are engaged in response to reward anticipation and reward attainment. In this vein, researchers have identified that in the anticipatory

[23] As illustrated in the figure, typically reward anticipation is modeled as the epoch between offset of the cue and onset of the target (when a fixation cross is shown), while reward attainment is modeled as the epoch in which feedback is displayed to the participant (Knutson & Greer, 2008).

[24] The foci listed above varied depending on whether the reward attainment contrast was defined as attainment of $1.00 vs. attainment of $50.00 reward, or attainment of magnitude of monetary reward vs. no reward.

phase of the Monetary Incentive Delay task the ventral striatum shows significant modulation based on the reward value of the trial during the period of reward anticipation (Knutson, Adams, et al., 2001), while a region in the medial prefrontal cortex (mPFC) preferentially tracks reward attainment (Knutson, Fong, Bennett, Adams, & Hommer, 2003). Indeed, more direct contrasts support this notion that there may be some slight variation in how reward anticipation vs. reward attainment processes recruit regions that lie along the trajectory of ascending dopamine projections (Knutson, Fong, et al., 2001).

There are two other advantages of the MID task paradigm worth discussing. First, the MID task is that has been studied extensively over the last two decades, and findings regarding the neural circuits it engages have been replicated over several studies (see Knutson and Greer (2008) for a review). Second, the MID task has shown sensitivity to differences between psychiatric patients and controls across a variety of disorders (e.g. depression Knutson, Bhanji, Cooney, Atlas, and Gotlib (2008), schizophrenia Juckel et al. (2006), substance use disorders Balodis and Potenza (2015)) as well as constructs like impulsivity (e.g., Plichta and Scheres (2014)). Evidence of this sensitivity to psychopathology and individual differences across individuals suggests that contrasts derived from the MID task are likely to be sensitive to differences across individuals in levels of higher-order factors of psychopathology.

1.5 Reward and psychopathology

Altered reward processing is a feature in multiple forms of psychopathology. Indeed, abnormal functioning of reward processes has actually been instantiated in the diagnostic criteria of several DSM-5 disorders: anhedonia in mood disorders; aphathy in schizophrenia; urges, cravings and abnormal valuations in substance use disorders; and low valuation of social reward in schizoid personality disorder and autism, to name a few (Zald & Treadway, 2017). However, there is still much controversy in regards to the best theoretical model to account for reward dysfunction in psychopathology.

In this section, I will review several case-controlled studies testing hypotheses of hyper- or hypo-responsivity to reward across a variety of DSM-ICD disorders. It is important to keep in mind that this is a vast literature comprising several different types of evidence, ranging from studies reliant on self-reports to studies focused on behavioral, neuroimaging or EEG measures. These different types of evidence do not always necessarily converge with one another, and they all provide valuable information. However, for the purposes of narrowing down the review to the aspects most pertinent to the study at hand, my review will be mostly focused on neuroimaging data.

Following this review, I will then attempt to integrate these data, as well as other evidence reviewed in this introductory chapter, to formulate some broad hypotheses to be tested in regards to how higher-order psychopathology factors might be associated with differences in brain response to reward anticipation and attainment in the MID task.

1.5.1 Hypotheses and evidence linking psychopathology to hypo-responsivity to reward

On one hand, several researchers have focused on testing the hypothesis that psychopathology might be associated with a global reduction in reward processing. Here, I will discuss four disorders for which this hypothesis has been formulated and tested extensively: addiction disorders, major depressive disorder (MDD; sometimes, more specifically anhedonia), attention deficit / hyperactivity disorder (ADHD), and schizophrenia[25].

Addiction. Within the context of the addiction literature, Blum et al. (1996) hypothesized that part of the etiology of addiction can be explained by a reward deficiency syndrome (RDS). The RDS hypothesis posits that a lack of rewarding subjective experiences or a reduced hedonic tone would lead individuals to pursue and consume strong rewards,

[25] I would like to acknowledge here that, although some past studies of higher-order psychopathology have included patients with psychosis in the estimation of a thought-disorder and/or general factor, the Tennessee Twin Study sample studied in this manuscript did not. Our sample specifically excluded patients with psychotic disorders. However, given the hypothesis postulated by Caspi et al. (2014) that psychosis might reflect the highest range of general psychopathology factor scores, I am including here a cursory review of these data for the sake of completeness.

such as drugs of abuse. Blum and colleagues linked RDS to neuroimaging data showing reduced striatal D2 dopamine receptor (DRD2) density in participants with substance use disorders, (Blum et al., 1996, 2000), as well as findings from N. Volkow et al. (1997) that there is lowered psychostimulant-induced dopamine release in patients with substance use disorders (Blum et al., 2000).

There is some empirical support for the RDS hypothesis in addiction studies. Two meta-analyses of human neuroimaging studies observed some degree of decreased striatal activation during monetary reward anticipation in addicted samples (Balodis & Potenza, 2015; Luijten, Schellekens, Kühn, Machielse, & Sescousse, 2017), and some pre-clinical animal studies are consistent with the hypothesis that lowered striatal DRD2 levels increase risk for drug self-administration (Nader et al., 2006). However, as articulated by Zald and Treadway (2017), there are several elements of the RDS hypothesis that are difficult to integrate with existing data. First, conceptualizing RDS as decreased reward anticipation seems rather incongruent with the DSM definitions of substance use disorders, which emphasize the willingness to spend excessive amounts of time, money and energy to pursue the rewarding drug or rewarding object. Second, conceptualizing RDS as a deficiency in reward attainment experience seems unlikely to drive substantial reward seeking; by devaluing a stimulus, e.g. devaluing food through satiation, a person should work less, not more, for it. This conceptualization is also inconsistent with findings from the above cited meta-analysis by Luijten et al. (2017), which found that addicted populations showed increased ventral striatum activation in the reward attainment phase. Third, although one might also consider conceptualizing RDS as a lowered homeostatic level of satisfaction, this alternative conceptualization finds limited support by the data, which emphasize that heightened negative and positive affect states play a stronger role in driving urges for drug consumption (Baker, Morse, & Sherman, 1986; Brandon, Wetter, & Baker, 1996; Zald & Treadway, 2017). Fourth, the linkage between RDS and dopaminergic function is inconsistent with mounting evidence showing that dopamine is more critically involved in reward

anticipation / motivational aspects as opposed to reward attainment. Indeed, significant work in animals and humans has shown that lowered expression of DRD2 receptors is not linked to reward attainment (Berridge & Robinson, 1998; Treadway & Pizzagalli, 2014; Zald & Treadway, 2017). Alternatively, if DRD2 were a marker of reward anticipation sensitivity, then addicted populations with lower DRD2 levels should have reduced wanting of drugs as opposed to craving, based on the findings cited above (Zald & Treadway, 2017).

Major depressive disorder. There is also some evidence linking hypo-responsivity to reward and depression. In a neuroimaging study, Pizzagalli et al. (2009) found that, relative to healthy controls subjects, participants with major depression showed significantly weaker response to gains in the left nucleus accumbens and caudate bilaterally, specific to reward attainment. In terms of reward anticipation, they found that participants with major depression showing reduced activation to reward cues in a small sector of the left posterior putamen. In another study, Kumar et al. (2008) found that patients with major depression had significantly reduced reward learning signals in several regions involved in the reward network, including the ventral striatum, rostral and dorsal anterior cingulate cortex, the midbrain and the hippocampus. Yet another study by Greenberg et al. (2015) found that in depressed individuals, greater anhedonia severity was associated with reduced reward expectancy and prediction error-related ventral striatal reactivity. Integrating a wide array of studies like these, in a meta-analysis of neuroimaging case-controlled studies looking at major depression, W. N. Zhang, Chang, Guo, Zhang, and Wang (2013) also found that patients with MDD tended to show decreased activation in the caudate during both reward anticipation and reward attainment. Intriguingly, these patients also tended to exhibit increased activation during reward anticipation in more frontal regions, such as the middle frontal gyrus, anterior cingulate cortex, and the frontal lobe.

Schizophrenia. Patients with schizophrenia have also shown decreased activation in reward circuit brain regions in neuroimaging studies. Juckel et al. (2006) found that unmedicated men with schizophrenia showed reduced ventral striatal activation during the

reward anticipation phase, compared to controls. Furthermore, the authors also found that decreased activation of the left ventral striatum was inversely correlated with the severity of negative symptoms. In another study, Morris et al. (2012) compared responses between expected and unexpected rewards in a conditioned cue paradigm for patients with schizophrenia and controls; they found that patients with schizophrenia did not display the normal differential activation between expected and unexpected rewards, which was in part due to blunted responses in the left ventral striatum to unexpected rewards - although, another part of this effect was due to exaggerated responses to reward attainment in the right ventral striatum.

ADHD. Reward deficiency hypotheses have also been prominent in neuroimaging studies of ADHD. A meta-analysis of case-controlled fMRI studies of ADHD patients found that ADHD patients have decreased activation of the ventral striatum relative to controls in the reward anticipation, with an overall estimated medium effect size (Cohen's *d* of .45 for all studies, and .58 when only including studies using the MID task paradigm) (Plichta & Scheres, 2014). According to Zald and Treadway (2017), this result may be associated with heightened temporal discounting of reward in ADHD patients, given evidence that in adolescents lower ventromedial caudate responses during reward anticipation are associated with steeper rates of temporal discounting behavior (Benningfield et al., 2014; Zald & Treadway, 2017). Other findings supporting a reward deficiency hypothesis for ADHD include observations that individuals with ADHD need greater incentives to modify their behavior (Kollins, Lane, & Shapiro, 1997) and positron emission tomography (PET) imaging studies showing adult individuals with ADHD have reduced function in the brain dopamine reward pathway (N. D. Volkow et al., 2011). However, as noted by Zald and Treadway (2017), there are some concerns with a global reward deficiency model for ADHD, particularly the fact that reward has robust effects on task performance for ADHD patients, and in some cases these effects can be even stronger for children with ADHD than typically developing children (Luman, Oosterlaan, & Sergeant, 2005; Zald & Treadway,

2017).

1.5.2 Hypotheses and evidence linking psychopathology to hyper-responsivity to reward

On the other hand, another line of research has tested an opposite hypothesis: that certain forms of psychopathology might be associated with a global hyper-responsivity to reward. Here, I will review these hypotheses with reference to addiction, bipolar disorder, and anti-social personality disorder.

Addiction. There is evidence that striatal activity is increased in the presence of drug-related cues (Leyton & Vezina, 2013), which is consistent with the excessive pursuit of drugs by addicted individuals despite their substantial costs or associated risks in addiction phenotypes (Zald & Treadway, 2017).

Bipolar disorder. Hyper-responsivity to reward has also been associated to bipolar disorder, although again there are some inconsistencies in terms of to which reward process these hyper-responsivities correspond. In one study, euthymic Bipolar I patients were found to display greater activation of the ventral striatum and right OFC in the reward anticipation phase, but not the reward attainment phase, of a card guessing task (Nusslock et al., 2012). In another study, remitted Bipolar I patients completed both the MID task and a Social Incentive Delay variant that administered social reward (via complements to the participant); contrary to the first study I discussed, this study found that remitted Bipolar I patients had elevated reactivity to the monetary and social reward attainment in the striatum relative to control, with no differences relative to controls in reward anticipation (Dutra, Cunningham, Kober, & Gruber, 2015).

Antisocial traits. A large number of higher-order psychopathology models, including the one specified in this study, have included psychiatric constructs associated with anti-social traits in specifications of an externalizing factor (i.e. oppositional-defiant disorder for youth, conduct disorder for adolescents and anti-social personality disorder or psychopathic traits measures for adults). There is evidence showing that these traits might be

associated with a hyper-responsivity to reward. For example, Buckholtz et al. (2010) found that in adults, impulsive-antisocial psychopathic traits were positively associated with the level of ventral striatal response in the reward anticipation phase of the MID task, and with nucleus accumbens dopamine release in response to pharmacological reinforcers. However, these findings are not fully congruent with another study looking at an adolescent sample: Bjork, Chen, Smith, and Hommer (2010) found that adolescents with externalizing disorders[26] showed significantly elevated nucleus accumbens activation in response to reward attainment. There are two potential things to keep in mind when looking at these paradoxical findings: first, differences in brain development across the populations of these two studies could explain the inconsistent result; second, the specific construct examined by Buckholtz et al. (2010) (impulsive-antisocial psychopathic traits) is more narrow and perhaps contained within the broader diagnostic categories of conduct disorders. Still, in spite of the contradictions, both of these studies offer some degree of evidence that antisocial traits might be associated with a hyper-responsivity to reward.

1.5.3 Possible hypotheses concerning links between reward processing and higher-order psychopathology

Several of the examples discussed above illustrate how simple global hyper- or hypo-reward processing models have been insufficient to explain the empirically observed alterations in reward processing across DSM-ICD disorders. Furthermore, the examples above suggest there is a lack of specificity among the abnormal reward function patterns observed across disorders; e.g., hyper- or hypo-activation of the ventral striatum in response to reward anticipation or attainment is a common theme across DSM-ICD disorders. These current limitations in the literature could be explained in a variety of ways. One possibility,

[26]To clarify, Bjork et al. (2010) primarily meant by this construct children who were diagnosed with disruptive, impulse control and conduct disorders. This can be ascertained by examining the breakdown of the adolescents with externalizing disorders group ($N = 12$) consisted of 6 adolescents with ODD, 3 adolescents with CD, 2 adolescents with co-morbid ODD and ADHD, and 1 adolescent with ADHD only.

suggested by Zald and Treadway (2017), is that that for the field to progress, we need to move past simple global hypotheses about hyper- or hypo-responsivity to reward and develop more refined or nuanced models of reward. Another possibility, which I will attempt to explore in this manuscript, is that the DSM-ICD constructs offer too narrow of a picture to fully understand the relationships between reward and psychopathology, which may be hierarchically organized and complex.

Taking into account the limitations of DSM-ICD approaches and the support for higher-order dimensional models of psychopathology, Lahey et al. (2017) have more formally postulated a "hierarchical causal taxonomy of psychopathology" that might provide a useful new framework to examine the relationship between psychopathology and neural markers of reward. In Lahey and colleagues' model, the hierarchical higher-order structure of psychopathology (discussed in Section 1.1) mirrors a hierarchy of increasingly specific etiologic influences. Thus, the general factor of psychopathology would be associated with the broadest, least-specific etiological factors that increase risk for all kinds of psychopathology, the internalizing/externalizing factors would be associated with etiological factors that increase risk more specifically for those spectra of disorders, and then going down the hierarchy, there would also be etiological influences that are disorder-specific or even symptom-specific. Applying this hierarchical approach to neuroimaging MID task data in a large sample has the potential to reveal neural substrates that might non-specifically contribute to multiple forms of psychopathology and their co-morbidity; and, in doing so, facilitate the study of mechanisms that are specific to single dimensions and subsets of symptoms (Zald & Lahey, 2017).

The purpose of my study is thus to examine the relationship between neural responses to reward anticipation and reward attainment in the MID task and higher order psychopathology factors as estimated using a bi-factor model. To achieve this, I analyzed data from Wave II of the Tennessee Twin Study (TTS). All participants in the TTS Wave II sample ($N = 499$) completed the computer-assisted YA-DISC psychopathology clinical interview,

and a subset of participants ($N = 448$) also completed a neuroimaging protocol that included the MID task. I used MID task data to compute reward anticipation and reward attainment activation maps for the $N = 326$ subjects with valid neuroimaging data (that passed a quality assurance protocol). I then conducted between-subjects analysis that tested for regional associations in the brain between higher-order psychopathology factors and activation in the reward anticipation contrast for the MID, by using a voxel-wise SEM approach. For each voxel in the brain, I specified a structural equation model that would allow me to test whether paths between higher-order psychopathology factors (general, internalizing, externalizing; estimated from the YA-DISC dimension symptom counts) and the MID reward anticipation activation measure were significantly different than zero. To correct for multiplicity, I used a clustering correction approach, which allowed me to identify clusters of voxels in the brain that showed significant associations to higher-order psychopathology. I subsequently used the exact same approach to examine relationships between higher-order psychopathology factors and activation in the reward attainment contrast of the MID task.

At a voxel-wise level, *my main hypothesis is that the general, internalizing and externalizing higher-order factors will show significant associations with activation to reward anticipation and attainment in the MID task*. At a brain-wide level, *I would expect that clusters of voxels showing significant associations with higher-order psychopathology would specifically localized to voxels corresponding to brain regions in the reward network*, including regions in the core reward circuit (e.g., striatum, ACC, OFC, pallidum) and regions that are not in the core circuit but are known to play a role in its regulation (e.g., PFC, amygdala, hippocampus, thalamus, insula, etc.).

I base this hypothesis on four premises. First, the higher-order factors estimated in the bi-factor model of psychopathology appear to be a viable metric of subjects' transdiagnostic disposition to experience psychopathology, as evidenced by studies supporting the criterion validity of the bi-factor model higher-order dimensions and supporting the emergence of a genetic general factor (Section 1.1). Second, higher-order dimensions of

psychopathology have been shown to be associated with structural and functional changes in brain regions associated with core executive function and reward processing (Section 1.2). Third, there is substantial evidence supporting the distinction between reward attainment and anticipation (Section 1.3) and that these two processes differentially and robustly recruit brain regions in the reward network (Section 1.4), particularly so in the MID task paradigm that was used in this study (Section 1.4.1). Fourth, as discussed earlier in Sections 1.5.1 and 1.5.2, there is significant evidence that psychopathology leads to changes in neural response to reward anticipation and attainment, although the directionality of these changes is inconsistent across and even within these disorders.[27]

[27]For this reason, I do not provide a strong hypothesis regarding directionality here. Questions regarding how to make sense of directionality will be further addressed in the discussion section.

Chapter 2

Materials and methods

2.1 The Tennessee Twin Study Sample

In this study, I analyzed participant data from Wave II of the Tennessee Twin Study (TTS) dataset. The TTS was orchestrated in two waves. Wave I of the TTS was designed to test different models and hypotheses pertaining to the latent structure of psychopathology. Wave II of the TTS was designed as a follow-up to Wave I, with one of the intents being attempting to link higher-order psychopathology constructs previously identified in the TTS Wave I and other epidemiological samples to behavioral and neural markers.

2.1.1 Wave I

Participants in Wave I were selected to be representative of all 6- through 17-year-old twins born in Tennessee and residing in one of the state's five metropolitan statistical areas (Nashville, Memphis, Knoxville, Chattanooga and Bristol) during the data collection phase (2000-2001). From birth records identified by the Tennessee Department of Health, a random sample was selected and stratified by age and geographic subareas, proportional to the number of families in each subarea. 4,012 household were selected to participate in the study; of these, 89.5% were located and screened. Of the screened families, 2,646 were found eligible based on pre-established criteria (both twins lived together with the adult caretaker for least half of the time in the past 6 months, and the twins and caretaker spoke English). Phone interviews were completed with 2,063 adult caretakers (90.8% biological mothers), with a 70% response rate. Twin pairs in which either youth had been diagnosed with autism, psychosis, or seizure disorder were excluded. After exclusions, the finalized sample consisted of 3,990 twins in 1,995 complete pairs. Caretakers classified 71% of the twins as non-Hispanic white, 24% African American, and 5% as Hispanic and other groups

(Lahey et al., 2008).

2.1.2 Wave II

Because of the high cost of collecting neuroimaging and lab data, a smaller sub-sample of twins previously surveyed in Wave I was invited to participate. Two important decisions were made when selecting this sub-sample. First, the age range was constrained to twins who were 10- to 17-year-olds during Wave I in order to narrow the age distribution. Second, high-risk twins were over-sampled based on Wave I CAPS psychopathology in order to ensure that there was enough representation of psychopathology in the smaller sub-sample. High-risk pairs were selected if either twin had symptom counts on the total number of internalizing, ADHD, or the combination of ODD and CD in the top 10% for that age range (Lahey et al., 2018).

A sub-sample of 405 twin pairs were invited to participate in Wave II. Of these, 40 pairs could not be located, or declined to be screened, and 18 selected pairs were declared out of scope due to previous participation in the pilot study, mental or physical incapacity, residence outside of the United States, current imprisonment, or death. This resulted in 347 total twin pairs (694 individual twins) who agreed and were deemed eligible to complete the telephone screening. During telephone screenings, 114 twin pairs were deemed ineligible to complete the neuroimaging portion for safety reasons (e.g., large body size, metal implants, claustrophobia), although they were still invited to complete interview assessments in person or by telephone (Lahey et al., 2018).

In total, of the 694 screened individuals, 499 completed clinical interviews either in person or over the phone for Wave II. These 499 individuals in the final Wave II sample contain 248 complete twin pairs (49.6% monozygotic; 66.9% high risk), and three individuals who interviewed without their twin (Lahey et al., 2018). Demographic characteristics for Wave II participants who completed clinical interviews are shown in Table 2.1, reproduced from a previously published paper by our group (Lahey et al., 2018).

Demographic variable	Percent/mean (SD)
Sex (% female)	52.1
Race-ethnic group	
Non-Hispanic White (%)	71.5
African-American (%)	25.2
Other groups (%)	3.2
Monozygotic twin (%)	49.5
Still in school (%)	26.0
Age	
In Wave I (mean, SD) (%)	13.6 (2.6)
In Wave II (mean, SD) (%)	26.9 (1.8)
Range in Wave II (%)	23-31
Years of education completed (mean, SD)	14.3 (2.3)

Table 2.1: Demographic characteristics for Wave II sample ($N = 499$), reproduced from Lahey et al. (2018)

The Vanderbilt University Institutional Review Board (IRB) reviewed and approved the TTS Wave II study protocols. Separate protocols were reviewed and approved by the IRB for participants who were and were not tested at Vanderbilt, and for those who did and did not complete an MRI session.

Participants who were tested at Vanderbilt read and signed informed consent forms. The TTS Wave II Vanderbilt lab visit consisted of a full day, 7-hour-long session, which included completion of several questionnaires, behavioral tasks, and an optional 1.5-hour functional and structural neuroimaging session. Participants who came in for the lab visit and completed MRI scanning were paid $400, plus up to $50 in task earnings. Participants who came in for the lab visit, but did not complete MRI scanning were paid $200 for participation in the study, plus up to $8 in task earnings. All of these participants were also reimbursed for travel expenses, and they were also eligible to earn $20 more by completing questionnaires at home.

Participants who were not tested at Vanderbilt (i.e., completed their psychiatric interview over the phone) provided verbal consent prior to initiating their phone interview, and

would then mail a signed consent form to the lab.[1] They would then spend about 2 hours completing a phone administration of the YA-DISC and filling out self-report forms. Participants not tested at Vanderbilt were paid $100 for complete participation in the study, with the potential to earn an additional $15 if they mailed back a saliva sample to the lab.

This study was funded by the National Institute of Mental Health, as part of it's Research Domain Criteria (RDoC) program. The NIMH has determined that phenotypic data collected for studies funded by the RDoC program should be provided to a data repository. In compliance with this policy, non-genetic data collected in Wave II of the TTS are currently stored on a platform specially created for RDoC projects by NDAR (ndar.nih.gov). Other researchers may request access to the TTS Wave II data being analyzed in this study, subject to approval by the NIMH.

2.2 Tasks and measures

2.2.1 Young Adult Diagnostic Interview Schedule (YA-DISC)

Psychopathology was assessed in Wave II using the Young Adult Version of the Diagnostic Interview for Children (YA-DISC) (Schaffer, Fischer, Piacentini, & Lucas, 2008).

The computer-assisted YA-DISC interview was selected due to mirroring several of the assessed dimensions in Wave I, and having a relatively low number of skip-outs. Skip-outs refer to heuristics used in many structured interviews, in which absence of one or two "main criteria" leads the interviewer to skip assessment of other symptoms in that dimension. While skip-outs like these might be useful heuristics in a clinical setting when attempting to arrive at a diagnosis, they can be problematic when attempting to model higher-order psychopathology, since they can artificially lower symptom counts. For this reason, selecting a clinical assessment instrument with low number of skip-outs like the

[1] Participants would receive two copies of the consent form in the mail prior to their phone interview; then, when a phone interview was scheduled, research assistants went over the consent with them, answered any questions they might have, and asked them if they agreed to participate in the study. If they agreed, these participants would then sign the consent form and mail a signed copy to the lab.

YA-DISC is important when modeling higher-order psychopathology.

The YA-DISC assessed for symptoms of ADHD, MDD, GAD, Post-Traumatic Stress Disorder (PTSD), Agoraphobia, Panic Attacks, Social Phobia, Specific Phobia, Manic Episodes, and Anti-Social Personality Disorder (APD), and maladaptive use of drugs such as nicotine, alcohol and marijuana during the past 12 months (Lahey et al., 2018).

2.2.2 Neuroimaging

The neuroimaging protocol lasted approximately 1.5 hours. Imaging data were acquired on two identical 3T Phillips Intera-Achieva MRI scanners, using a 32-channel head coil. We ensured that both twins in any pair were scanned in the same scanner (i.e., twin pairs are nested within scanners).

T1-weighted anatomical structure images (used in our processing pipeline for registration purposes) were acquired with a 3-D Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence, with the following parameters: TE/TR = 9000/4600ms; SENSE = 2.0; echo train = 131; scan time = 4 min 32 s; FOV = $256 \times 256 \times 170$mm; flip angle = 5°; 1mm isotropic voxel resolution.

Functional data for the Monetary Incentive Delay task were collected across 3 functional runs with identical scanning parameters: TR/TE = 2000/28ms; SENSE = 2.0; echo train = 43; scan time = 8 min 12 s; volumes = 246; FOV = $80 \times 80 \times 38$; flip angle = 15°; 3mm $\times$ 3mm $\times$ 3.30mm voxel resolution.

In the same session, participants also completed functional runs of a Go/No-Go task (2 runs), a Cued Aversive-Threat Picture Task (2 runs), and a diffusion weighted imaging (DWI) scan. These tasks and scans will not be discussed in this thesis.

2.2.3 Monetary Incentive Delay (MID) task

The TTS Wave II study used an adapted version of the Monetary Incentive Delay (MID) task (Knutson et al., 2000; Knutson, Adams, et al., 2001) to assess reward anticipation and

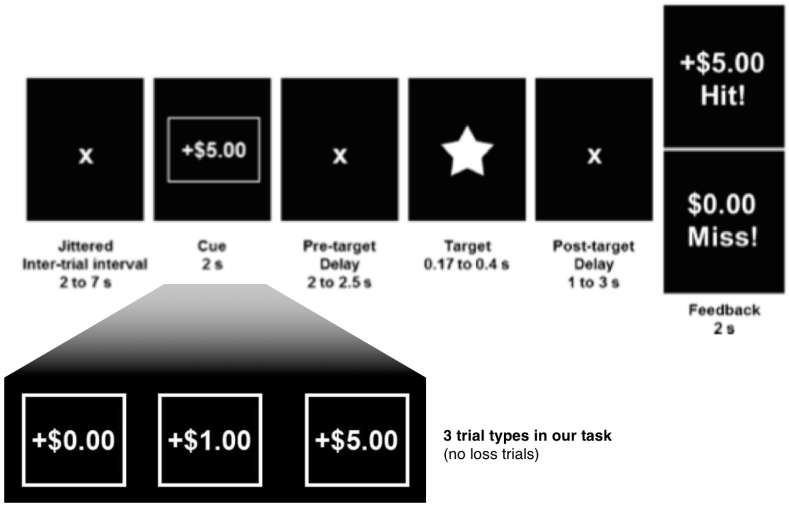

Figure 2.1: Trial structure in TTS Wave II MID task, adapted from Knutson et al. (2000)

response to reward attainment. As discussed earlier (see Section 1.4.1), the MID is one of the most widely used measures of individual differences in corticostriatal reward circuitry. The structure of our version the task can be seen in Figure 2.1. In each trial, participants saw a cue indicating the reward value of the trial (in the TTS MID task adaptation, the cue consisted of a numeric cash value with a plus sign, as opposed to other trials that use circles or squares crossed with lines to indicate the value of the upcoming trial). Following a variable delay period, participants then had to make a rapid response to a target in order to obtain the monetary reward indicated in the cue. A few seconds after the target disappeared, participants were then informed of whether they hit or missed the target, and the amount of money they earned in that trial. In the TTS MID task adaptation, there were three possible conditions for each trial: +$5.00, +$1.00, or +$0.00 (no gain / control); there were no punishment or loss conditions included. Participants completed 3 runs of the MID task, each of which contained 13/13/14 trials for each condition, which amounted to a total of 40 trials per condition across runs.

2.2.4 Urine drug screen

To assess whether participants were or had recently been under the influence of psychoactive substance, participants were required to complete a urine drug screen. Most participants in the TTS Wave II study were screened using a urine dip strip manufactured by Medimpex United, Inc. (SKU: DTP-10), which screened for amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, methamphetamine, methadone, opiates, and phencyclidine. A few participants, however, were screened with a urine dip strip by USHealthTests, Inc. (SKU: IS10), which tested for all of the drugs listed earlier and tricyclic antidepressants.

2.3 Neuroimaging pre-processing pipeline

Of the 499 individuals who completed Wave II clinical interviews, a total of 448 individuals consented to the neuroimaging protocol and participated in a scanning session.

As it pertained to our analysis of the MID task, we excluded 14 of these 448 participants prior to the data processing phase based on review of the scanning logs kept by research assistants and the available data. Reasons for exclusions are outlined as follows: 1 participant was excluded due to reporting suffering from a very strong migraine during the task; 1 participant was excluded due to reporting suffering from strabismus during the task; 4 participants were excluded due to missing scan or task data; 2 participants were excluded due to not responding to the task or falling asleep; and 6 participants were excluded because their scans were interrupted (e.g., due to claustrophobia, technical problems, nausea or other factors).

The functional and structural data for the remaining 434 subjects were compiled into a dataset compliant with the Brain Imaging Data Structure (BIDS) (K. J. Gorgolewski et al., 2016). Our dataset was then pre-processed using the FMRIPREP v1.0.0 pipeline (Esteban et al., 2018). Following is a detailed description of the pre-processing steps, generated by

the FMRIPREP program based on our input processing parameters:

> Pre-processing was performed using FMRIPREP version 1.0.0 (Esteban et al., 2018) a Nipype (K. Gorgolewski et al., 2011; K. J. Gorgolewski et al., 2017) based tool. Each T1 weighted volume was corrected for bias field using N4BiasFieldCorrection v2.1.0 (Tustison et al., 2010) and skull-stripped using antsBrainExtraction.sh v2.1.0 (using OASIS template). The skull-stripped T1w volume was coregistered to skull-stripped ICBM 152 Nonlinear Asymmetrical template version 2009c (Fonov, Evans, McKinstry, Almli, & Collins, 2009) using non-linear transformation implemented in ANTs v2.1.0 (Avants, Epstein, Grossman, & Gee, 2008).
>
> Functional data were slice time corrected using AFNI (Cox, 1996) and motion corrected using MCFLIRT v5.0.9 (Jenkinson, Bannister, Brady, & Smith, 2002). This was followed by co-registration to the corresponding T1-weighted volume using boundary-based registration with 9 degrees of freedom, implemented in FSL (Greve & Fischl, 2009). Motion correcting transformations, T1 weighted transformation and MNI template warp were applied in a single step using antsApplyTransformations v2.1.0 with Lanczos interpolation.
>
> Three tissue classes were extracted from T1w images using FSL FAST v5.0.9 (Y. Zhang, Brady, & Smith, 2001). Voxels from cerebrospinal fluid and white matter were used to create a mask that was in turn used to extract physiological noise regressors using aCompCor (Behzadi, Restom, Liau, & Liu, 2007). Masks were eroded and limited to subcortical regions to limit overlap with gray matter, six principal components were estimated. Frame-wise displacement (Power et al., 2014) was calculated for each functional run using Nipype implementation.

2.4 Neuroimaging quality assurance

Following successful pre-processing, these 434 Wave II participants were included in our quality assurance (QA) pipeline. Our QA pipeline consisted of the following steps.

1. The subject's anatomical and functional data were pre-processed using the FMRIPREP-v1.0.0 pipeline, the details of which are presented in the following section. Research assistants then reviewed the output reports produced by FMRIPREP for the subject, to ensure that normalization and brain mask estimation was accurate.

2. Stimulus timing data were used to create a design matrix for the subject's MID runs in SPM12 (fil.ion.ucl.ac.uk/spm/software/spm12).

3. A composite coverage mask was created for each subject by calculating the intersection of the coverage masks for each run produced by FMRIPREP.

4. The composite coverage mask, design matrix file and motion regressors (calculated by FMRIPREP) were fed into the ART Toolbox for SPM, version 2015-10 (nitrc.org/projects/artifact_detect). Outlier timepoints were then estimated by ART using the following thresholds: global signal $z > 3$; motion $>$ 1mm.

5. Runs were flagged for exclusion if 20% of TRs for any condition of interest (e.g., CueFive, CueOne, CueZero, FiveHit, FiveMiss...) were identified as outliers.

6. Subjects were flagged for exclusion if they had less than 2 viable runs (i.e., 2 or 3 of their runs were flagged for exclusions by the QA algorithm)

Head motion during scanning is one of the most problematic sources of artifacts in neuroimaging, because it can yield differences across participants' parameter maps that could easily be mistaken for neuronal effects (Van Dijk, Sabuncu, & Buckner, 2012). I decided to detect and censor outlier timepoints based on empirical evidence supporting timepoint censoring in fMRI. Motion censoring has been found to decrease variance in

parameter estimates within- and across-subjects, reduce residual error in GLM estimation, and increase the magnitude of statistical effects (Siegel et al., 2014). A 0.9mm framewise motion displacement threshold was chosen for flagging outliers because this specific threshold was found to be ideal in maximizing effect sizes in the aforementioned study[2].

An assumption of the within-subject GLM analyses used to obtain parameter maps for each condition is that residuals will be normally distributed after regressing out task and motion parameters. However, this assumption can be violated more often than one might think due to just a few outlier timepoints. In a study with 328 subjects and 3 runs per participant, Whitfield-Gabrieli (2017) found that in 48% of the sessions the residualized scan-to-change in average BOLD signal was not normally distributed. However, this percentage dropped to 4% when removing an average of 8 timepoints per run, using a global signal threshold of $z > 3$. Furthermore, she found that global signal outlier removal improved power to detect task effects from .29 (prior to censoring) to .70 (after censoring an average of 8 scans per session, using the aforementioned threshold). Given that censoring of a few timepoints can both reduce violations of assumptions of normality and improve power to detect effects, I decided to implement this procedure as part of my Quality Assurance pipeline. I chose the threshold of $z > 3$ because this was explicitly recommended by Whitfield-Gabrieli (2017), who also developed the ART Toolbox that is being used in our pipeline.

An important drawback from the censoring QA approach used in this paper is that it results in an effective reduction in the temporal degrees of freedom being used to estimate parameter maps for conditions of interest. That is, at a given threshold, the number of time-points being censored will be higher for subjects who move more, leading to fewer

[2]It is worth noting here that the study by (Siegel et al., 2014) flagged timepoints for censoring based on a *framewise displacement* (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012) global motion metric, which is very similar, but not exactly identical, to the *composite motion* metric used by the ART toolbox (for more on this, see nitrc.org/forum/forum.php?thread_id=4028&forum_id=1144). While general support for the concept of thresholding still holds, the optimal framewise displacement threshold of 0.9mm might correspond to a slightly different number in ART's composite motion metric. However, since no studies were done on the optimal metric to use with ART's composite metric, I am using the FD-optimal threshold, with the expectation that it should be a good approximation of the optimal value for ART's metric.

temporal degrees of freedom being available for estimating parameters maps. At a within subject level, the consequence of this is that the reliability and power of parameter estimates for those subjects will be reduced. On a between-subjects level, this becomes even more problematic because it could introduce biases. That is, if high motion covaried with higher-order psychopathology or other factors of interest, inclusion of these subjects at the group level could lead to biased estimates of group-level effects (Caballero-Gaudes & Reynolds, 2017). In order to avoid these potential biases, Caballero-Gaudes and Reynolds (2017) recommend setting a maximum number of censored volumes across populations included in a group analysis, in order to assure that there is some degree of consistency. This approach was taken here by setting an *a priori* threshold that no more than 20% of timepoints used to estimate parameter maps for a given condition of interest be flagged for censoring in the QA pipeline in order for a run to be included. This specific threshold, although somewhat arbitrary, is consistent with what has been used in other studies applying the censoring approach for modeling fMRI task data (Simmonds, Hallquist, & Luna, 2017).

2.5 Neuroimaging analyses: within-subjects (first-level)

Following pre-processing, each subject's data were smoothed using a 6mm full width at half-maximum (FWHM) Gaussian kernel using SPM12. Then, for each participant, AFNI's 3dDeconvolve was used to model the ideal hemodynamic response to each event type as a boxcar function convolved with a canonical hemodynamic response function. For each participant, I created a design matrix including regressors for signal drift, response to each task condition of interest, and six regressors for motion and rotation; in addition, regressors were added to censor TRs as guided by the neuroimaging QA in ART described above. An example of the design matrix specified by AFNI's 3dDeconvolve is shown in Figure 2.2.

Model estimation was conducted using 3dREMLfit, which performed Generalized Least Squares (GLSQ) regression combined with REML estimation of an ARMA(1,1) temporal

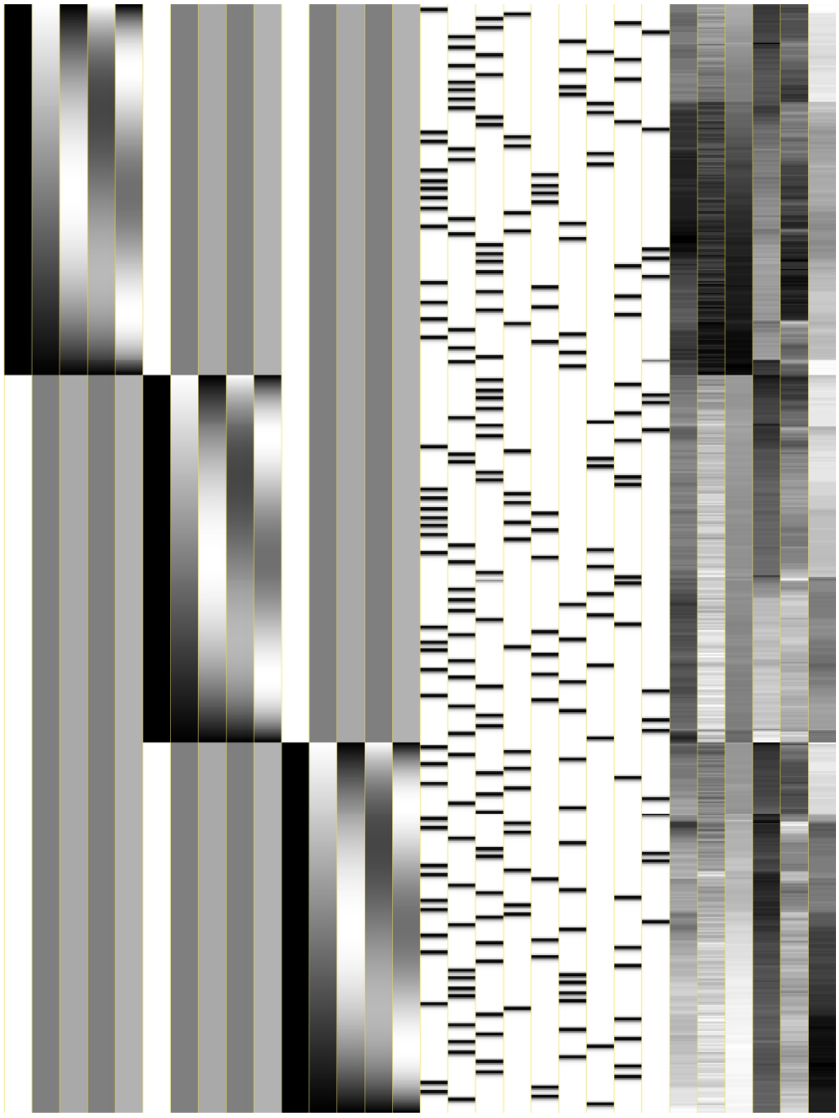

Figure 2.2: Example design matrix from 3dDeconvolve for a participant with three runs and no outlier timepoints. From left to right: the first 15 columns are polynomial regressors used to model run-specific baseline signal and signal drift, using polynomials (5 columns per run). The following 9 columns correspond to parameter estimates for task conditions of interest: anticipation of \$5, \$1, \$0 trial; hit \$5, \$1, \$0 trial; miss \$5, \$1, \$0. The last 6 columns correspond to regressors for 3-D motion displacement (x, y and z axes) and 3-D head rotation, estimated by FMRIPREP during re-alignment of the images. If a participant had a censored timepoint, an additional column would be tacked at the end, with a value of 1 for the censored TR and 0 for all others.

correlation structure. For each subject, I also modeled within-subject contrasts of interest in this stage, which were specified as General Linear Tests (GLTs):

1. Anticipation: \$5 trial − \$0 trial (high vs. no reward)
2. Attainment: \$5 hit − \$5 miss

2.6 Neuroimaging analyses: between-subjects (second-level)

2.6.1 Issues considered when selecting a between-subjects analysis approach

Both the nature of the TTS Wave II sample and my interest in examining relationships with latent constructs led to some unique challenges when coming up with a between-subjects analysis approach:

- *Sampling issues*. The TTS Wave II sample is not a random sample. Subjects represented in Wave II include those who were selected based on over-sampling for psychopathology from TTS Wave I respondents, and is further limited to those who were both eligible to participate in the study and chose to participate.
- *Non-independence*. The TTS Wave II sample consists of twins, which means there is high non-independence in the sample that must be statistically accounted for. Furthermore, the TTS Wave II sample twin pairs are heterogeneous in sex and relatedness, i.e., there are mono-zygotic twin pairs, di-zygotic twins of the same sex, and di-zygotic twins of different sexes. Again, this must be accounted for statistically.
- *Neuroimaging subsample*. Not all TTS Wave II participants came in for a lab visit, and were eligible for or completed the imaging protocol. Furthermore, not all TTS Wave II participants who completed the imaging protocol pass our QA pipeline, i.e. are eligible for inclusion in the between-subjects analyses.

- *Latent variables*. The constructs of interest are latent variables. This means that relationships between these constructs and neural response need to be analyzed either within an SEM framework, or by potentially extracting factor score estimates and then using another regression-based approach.

- *Voxel-wise analysis*. My intended goal with these analyses is to take a whole-brain, voxel-wise approach will be taken. This means that the regression model would be run for each voxel in the brain (there are 61,183 voxels in our between-subjects mask), with each of these 61,183 models having as a dependent variable the participants' contrast estimate for a given voxel. Because of this, I need to correct for multiplicity to avoid increased false positive rates. Furthermore, in using an SEM approach, I have to consider how introducing the voxel variable might affect the loadings in the bi-factor model, and therefore the extent to which this variability in the measurement model could affect the commensurability of results across voxels.

- *Software limitations*. Currently available mainstream neuroimaging software packages (AFNI, FSL, SPM) are not well equipped to handle complex designs with non-independence. The most sophisticated mainstream product available currently is AFNI's 3dLME, which allows for a Linear Mixed Effects model with one random intercept and one random slope (Chen, Saad, Britton, Pine, & Cox, 2013).

In choosing an approach, I realized it would be difficult for me to address every single challenge listed above optimally. I want to be upfront and acknowledge to the reader that the approach I am about to present is not perfect or the only approach that could be used. However, I believe this approach does address most of these issues to some extent. I will provide a more in-depth discussion on the strengths and limitations of my methodological approach, as well as future directions or improvements that could be made, in the Section 4.3.

2.6.2 Voxel-wise SEM approach

I chose to use a voxel-wise, Structural Equation Modeling (SEM) based approach to test my hypothesis that paths from general, internalizing and externalizing factors to the MID reward anticipation and reward attainment contrasts would be significantly different than 0. My approach consists of a two-step SEM, which is consistent with what my group has used in other analyses to test other neuroimaging related hypothesis in the TTS Wave II dataset (Hinton et al., 2019).

First, I ran a confirmatory factor analysis (CFA) in Mplus 8 (M. . Muthén, 2018) to obtain the un-standardized factor loadings for the bi-factor model that was previously identified by our group to have the best fit for the full TTS Wave II sample ($N = 499$) (Lahey et al., 2018). The model specification was almost identical to the one discussed in the aforementioned publication: I used maximum likelihood estimation with robust standard errors (MLR) to account for non-normality in symptom count distributions, and I instructed Mplus to adjust standard errors to reflect stratification in sampling and the clustering of twins within twin pairs. The one change in my analysis is that, unlike Lahey et al. (2018), I did *not* use weights to account for probability of selection into the Wave II sample or biases that may have emerged due to non-response or missing data in my CFA analysis.[3]

Second, for each voxel in the brain (61,183 total voxels), I specified a SEM analysis, again using Mplus 8. The SEM specification for a single voxel is illustrated in Figure 2.3. In all these SEMs, I fixed the loadings of higher-order psychopathology factors onto symptom count dimensions to be the unstandardized loadings obtained from the CFA of the full TTS sample described above. In each of these SEMs, the dependent variable was the z-scored contrast estimate for a single voxel[4]; the latent independent variables were the higher-order psychopathology factors (general, internalizing, and externalizing); and

[3]For further explanation of why this decision was made and what implications it has, please refer to the Section 4.3 in the Discussion chapter.

[4]The contrast estimates were large numbers, which created problems for Mplus when attempting to run the SEMs. To overcome these Mplus limitations, I z-scored contrast estimates for each given voxel, across all participants, for the same voxel.

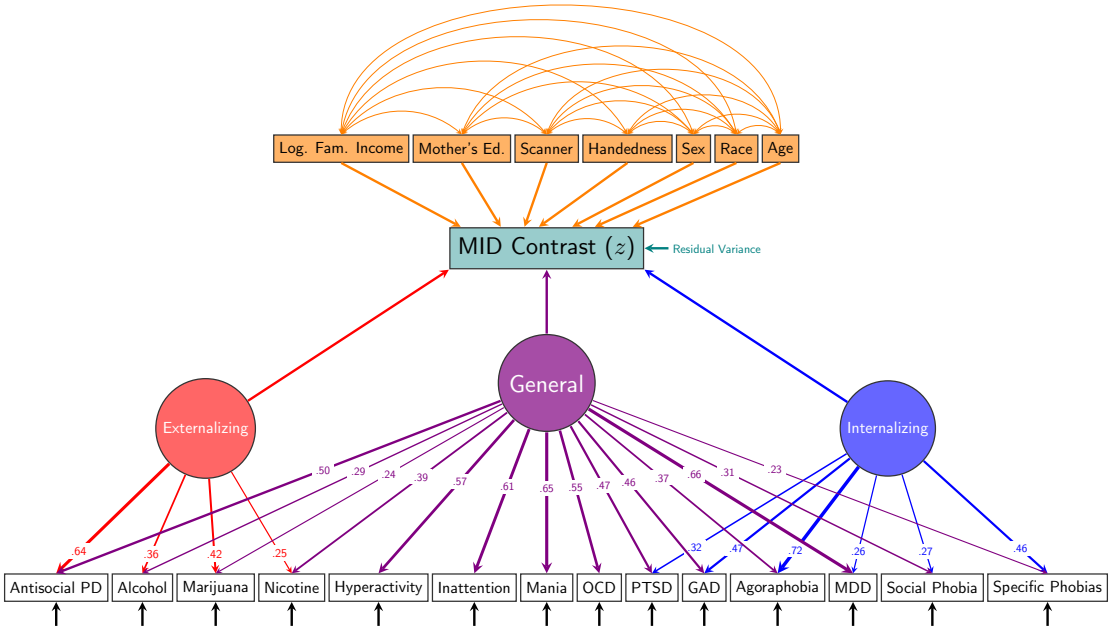

Figure 2.3: Example SEM specification for a given voxel. Note that the λ factor loadings for general, internalizing and externalizing are fixed to those obtained from running the model with the full sample ($N = 499$). I scraped the standardized (STDYX) output from Mplus to create brain maps of the standardized estimated path coefficient, its standard error and associated p-value for paths between the MID contrast and other variables.

several manifest independent variables were included as covariates: age, sex, race, scanner, mother's education, family income (log-transformed), and handedness. This SEM included only the subset of participants with viable fMRI data (in this case, $N = 326$). Similar to the first CFA step, for all SEMs I used maximum likelihood estimation with robust standard errors (MLR) to account for non-normality in symptom count distributions, and I instructed Mplus to adjust standard errors to reflect stratification in sampling and the clustering of twins within twin pairs.

From each of these SEMs, I exported Mplus outputs and integrated them into parameter maps of the betas, standard error, and p-values for each independent variable included in the SEM regression.

My scripts to achieve these SEM analyses were coded and run in R (R Core Team, 2013) version 3.5.1, and relied on two libraries. I relied on Neuropointillist (Madhyastha et al., 2018) to extract voxel-wise data for each voxel across subjects, generate data-frames on the fly, run my analysis script across subjects and organize the outputs of each voxel's SEM into standard NIFTI files[5]. I also relied on the MplusAutomation package (Hallquist & Wiley, 2018) to export data frames for each voxel to an Mplus compatible format, generate Mplus SEM scripts on the fly based on my template, and scrape Mplus outputs into an R data structure that could be saved using Neuropointillist.

2.6.3 Multiplicity correction approach

To address the issue of multiplicity (due to the large number of voxels in the brain), I followed the recommendation by the creators of Neuropointillist to use AFNI's cluster-based correction for multiple comparisons (Integrated Brain Imaging Center at the University of Washington, 2018). This approach consisted of the following steps. First, AFNI's 3dFWHMx was used on each subject's within-subject GLM residuals to estimate the pa-

[5]Neuroimaging Informatics Technology Initiative (NIFTI) is a popular 3D or 4D neuroimaging format for storing brain maps.

rameters of their spatial auto-correlation function (ACF).[6] This yielded a list of spatial ACF parameter estimates for each subject. These parameters were then averaged across subjects, and fed to AFNI's 3dClustSim program. 3dClustSim then ran 10,000 simulations in which it generated a 3D grid of independent and identically distributed $N(0,1)$ random deviates, smoothed them to the level estimated from the average spatial ACF parameters across subjects in our sample, carried out voxel-wise thresholding, and then finally clustered the voxel maps to determine how often contiguous clumps of varying sizes occur at various voxel-wise thresholds. From these simulations, 3dClustSim yielded a table that indicates the empirical cluster extent threshold obtained from the simulations corresponding to one's desired α and voxel-wise uncorrected p-value threshold (Cox et al., 2017). Based on an empirical examination of false positive rates obtained from this approach, Cox et al. (2017) recommend that in complex group analyses with mixed models, researchers use an uncorrected voxel-wise p-threshold of either $p = .001$ or $p = .002$. Based on this recommendation, I decided *a priori* that I would use a voxel-wise p-threshold of $p = .001$, and select the cluster-extent threshold corresponding to an empirical $\alpha = .05$. Clustering was done using the nearest neighbor (NN) definition recommended by the AFNI developers, which is $NN = 1$ (Cox et al., 2017).[7]

2.6.4 Manipulation check

The aforementioned analysis is predicated on the fact that the MID task was able to effectively engage the reward network in study participants. Although the MID task has

[6] According to Cox, Chen, Glen, Reynolds, and Taylor (2017), the empirical ACF estimates are typically fit well by a function that mixes a Gaussian and monoexponential form, which involves the estimation of 3 parameters.

[7] AFNI and 3dClustSim give the option of selecting from estimated cluster extent thresholds corresponding to different nearest neighbor (NN) definitions (i.e., what voxels are considered contiguous). AFNI provides three options for this: $NN = 1$, typically used by AFNI, which defines a contiguous voxel as one that shares a face with another voxel (i.e., 6 possible contiguous voxels); $NN = 2$, typically used by SPM, which defines a contiguous voxel as one that shares either a face or an edge with another voxel (i.e., 18 possible contiguous voxels); and $NN = 3$, typically used by FSL, which defines a contiguous voxel as one that shares a face, an edge or a corner (i.e., 26 possible neighboring voxels) (Cox et al., 2017).

been published on extensively and has replicated well across studies (see Section 1.4.1), a manipulation check was included to ensure that the task reliably engaged the reward network in our study sample.

The main obstacle for this manipulation check analysis was non-independence in the sample due to the twins, which I decided to address by splitting the sample such that no two relatives would be present in the same sample. I used R to pseudo-randomly separate each twin pair into two groups, such that no two related individuals would be in the same group. I then pseudo-randomly assigned "stray" twins (i.e., those for whom their twin was not scanned or was excluded in the QA procedure) equally amongst the two sub-samples.

Subsequently, I used AFNI's 3dttest++ to examine task effects in the contrasts I would be examining in relation to psychopathology. I did this in a voxel-wise fashion: for each voxel, I conducted a paired t-test in which I tested whether the β parameter estimates from the within-subject GLM for the two conditions being contrasted were equal. I then used the multiplicity correction approach outlined above in Section 2.6.3 to correct for multiple comparisons across voxels within each analysis.

AFNI's 3dttest++ also offers the option to account for covariates in the analyses (see bit.ly/2EjFLHU for further details on how covariates are accounted for by the program). In these manipulation check analyses, I also controlled for the same covariates used in the SEM at a between-subjects level: mother's education, log-transformed famimly income, age, sex, handedness, and scanner.

Chapter 3

Results

3.1 fMRI quality assurance results

A total of 326 participants out of 433 participants (75.28%) passed the QA pipeline based on our *a priori* thresholds (see Section 2.4). Of those subjects who passed the QA pipeline, 83 participants (25.46%) passed the QA protocol threshold for 2 our of 3 runs, while the remaining 243 participants (74.54%) passed the QA protocol for 3 out of 3 runs.

3.2 Demographics and psychopathology coverage of neuroimaging sub-sample

Table 3.1 compares the demographics of the $N = 326$ sub-sample of participants who survived the neuroimaging correction with that of all TTS Wave II ($N = 499$)[1]. As evidenced by Table3.1, the TTS Wave II sub-sample that survived QA is demographically quite similar to the broader sample.

Another aspect that was examined whether the representation of different symptom dimensions in the inclusion sub-sample might have differed from that of the full sample. This could have impacted the analyses by affecting the covariance matrix between disorders, which is essentially what the bi-factor psychopathology factor model is trying to reproduce. This was examined in a couple ways.

The first aspect that was examined was whether the sub-sample included individuals who had endorsed some symptoms in every dimension of psychopathology being considered. Figure 3.1 illustrates this comparison. As shown in the figure, the neuroimaging sub-sample that passed QA had very similar proportions of participants endorsing psychopathology as the full sample for most disorders.

[1]Handedness data is missing for 16 subjects in the broader sample; this proportion refers to the 483 subjects for which we have handedness data.

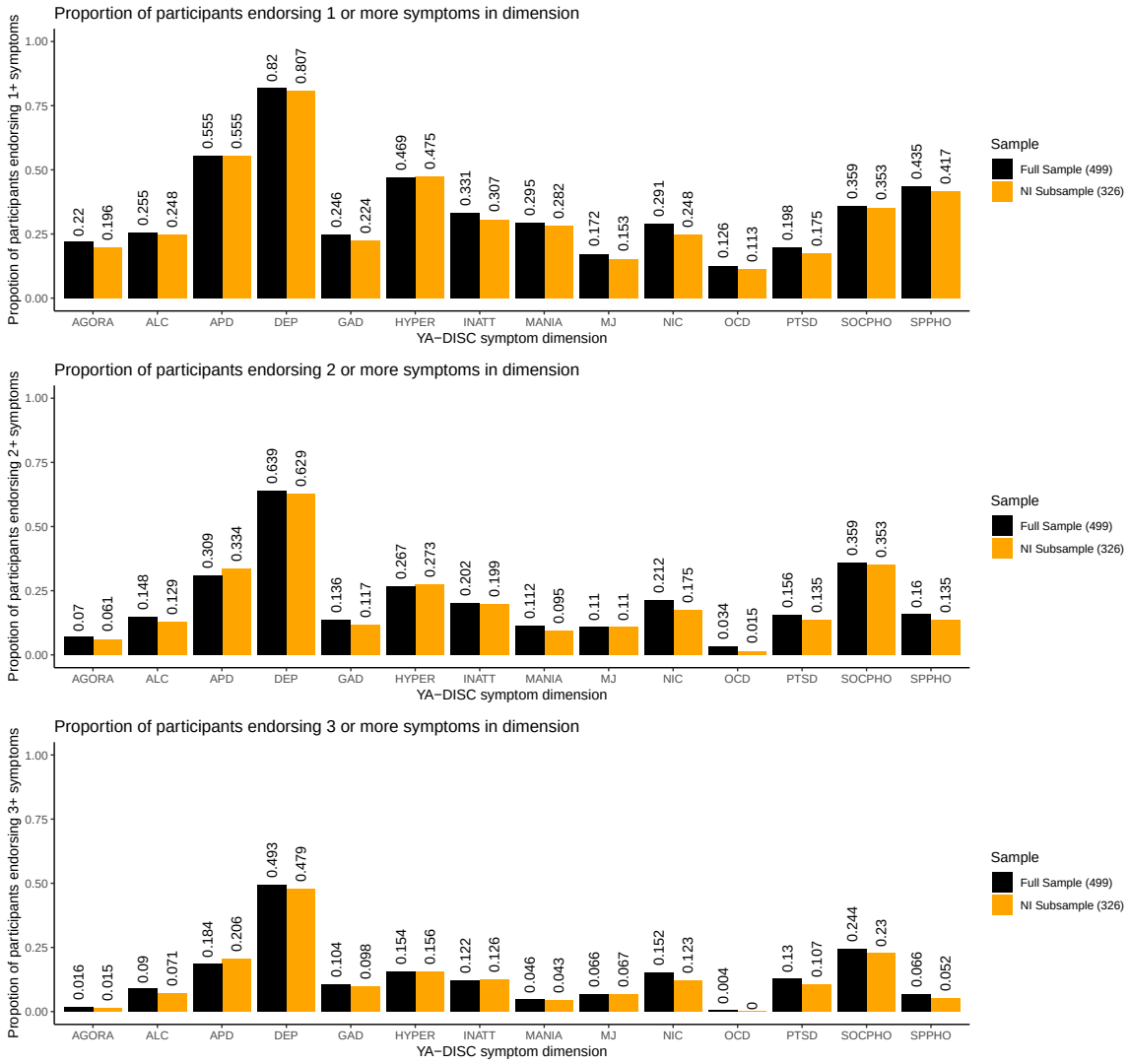

Figure 3.1: Comparison of symptom endorsement in full TTS Wave II sample and neuroimaging sub-sample. Proportions are calculated on the basis of the number of individuals in the sample/sub-sample who a number of symptoms greater than or equal to the threshold. Symptom dimensions are obtained from the YA-DISC. The top panel shows the proportion of participants endorsing one or more symptoms for a dimension; the center panel shows the proportion endorsing 2 or more symptoms for a dimension; and the bottom panel shows the proportion of participants endorsing three or more symptoms in a dimension.

Variable	Full sample ($N = 499$)	fMRI sub-sample ($N = 326$)
Sex (% Female)	52.10%	53.37%
Race (% Non-Hispanic White)	71.54%	75.15%
Handedness (% right-handed)	89.02%	91.10%
Age		
Mean $\pm$ SD	26.05 ± 1.80	26.03 ± 1.77
Range	$23-31$	$23-31$
(Log) Family Income		
Mean $\pm$ SD	2.86 ± 0.48	2.89 ± 0.44
Range	$0.00-3.18$	$0.00-3.18$
Mother's Years of Education		
Mean $\pm$ SD	13.59 ± 2.74	13.78 ± 2.75
Range	$0-20$	$0-20$

Table 3.1: Comparison of demographics for full TTS Wave II sample and neuroimaging sub-sample

The second aspect that was examined was whether the correlation matrices for symptom dimensions differed between the full sample and the neuroimaging sub-sample. Figure 3.2 illustrates the Spearman rank correlation matrices for the full sample ($N = 499$) and the neuroimaging sub-sample ($N = 326$), as well as the differences between these two matrices. Absolute differences between both correlation matrices ranged between 0.0001 and 0.1084. The mean absolute difference between correlation matrices was 0.036, with a standard deviation of 0.024. Differences between both correlation matrices ranged between -0.053 and 0.1084, with positive values indicating a larger correlation in the full sample relative to the neuroimaging sub-sample, and negative values reflecting a larger correlation in the sub-sample relative to the full sample. The largest differences between the full sample and the sub-sample were the correlation between marijuana use and nicotine use (0.26 in full sample, 0.15 in neuroimaging sub-sample; 0.11 difference) and the correlation between nicotine use and hyperactivity symptoms (0.25 in full sample, 0.15 in neuroimaging sub-sample; 0.10 difference). Aside from the two aforementioned correlations, no other Spearman rank correlations between YA-DISC symptom dimensions differed between the

full sample and the sub-sample by more than 0.10. Overall, while there are some differences in the correlation matrices between the broader sample and the included sub-sample, these differences are small in nature.

3.3 Manipulation check: task effects

I split the $N = 326$ sample of participants surviving QA into two sub-samples of $N = 163$ subjects each; within each sub-sample, no participant was related to one another. In this section, I will refer to each half as "half 1" (H1) and "half 2" (H2).

3.3.1 Reward anticipation contrast

For the \$5 trial vs. \$0 trial anticipation contrast, I found similar results across each half. Although I initially attempted to threshold the activation maps with the aforementioned strategy (uncorrected voxel-wise $p < .001$, cluster extent threshold $k = 34$), this was not effective for visualization purposes as it led to a massive, brain-wide cluster of over 40,000+ voxels across both samples that appeared to be too broad to be informative. This can tend to happen in neuroimaging studies that are overpowered for simple contrasts. For this reason, I thresholded the image using a more conservative threshold of $p < 10^{-28}$, which was more illustrative for visualization purposes.

In H1, thresholding with the aforementioned threshold led to the identification of a large cluster of 12,739 voxels (peak MNI coordinates $(0, -39, 1.2)$), where for all these voxels the beta for the BOLD signal in the anticipation of \$5 trial condition was higher than that of the \$0 condition. In H2, I found a very similar cluster of size 10,767 voxels, with the same exact peak MNI coordinates. The clusters for each half, entered on the peak region, are shown in Figure 3.3. Across both samples, these clusters included several regions in the reward network, including VS and VP, ACC, OFC, and insula. Additionally, this cluster included other areas involved in sensory and motor processing, including the pre-supplementary motor area (pre-SMA), motor cortex, visual cortex, and cerebellum.

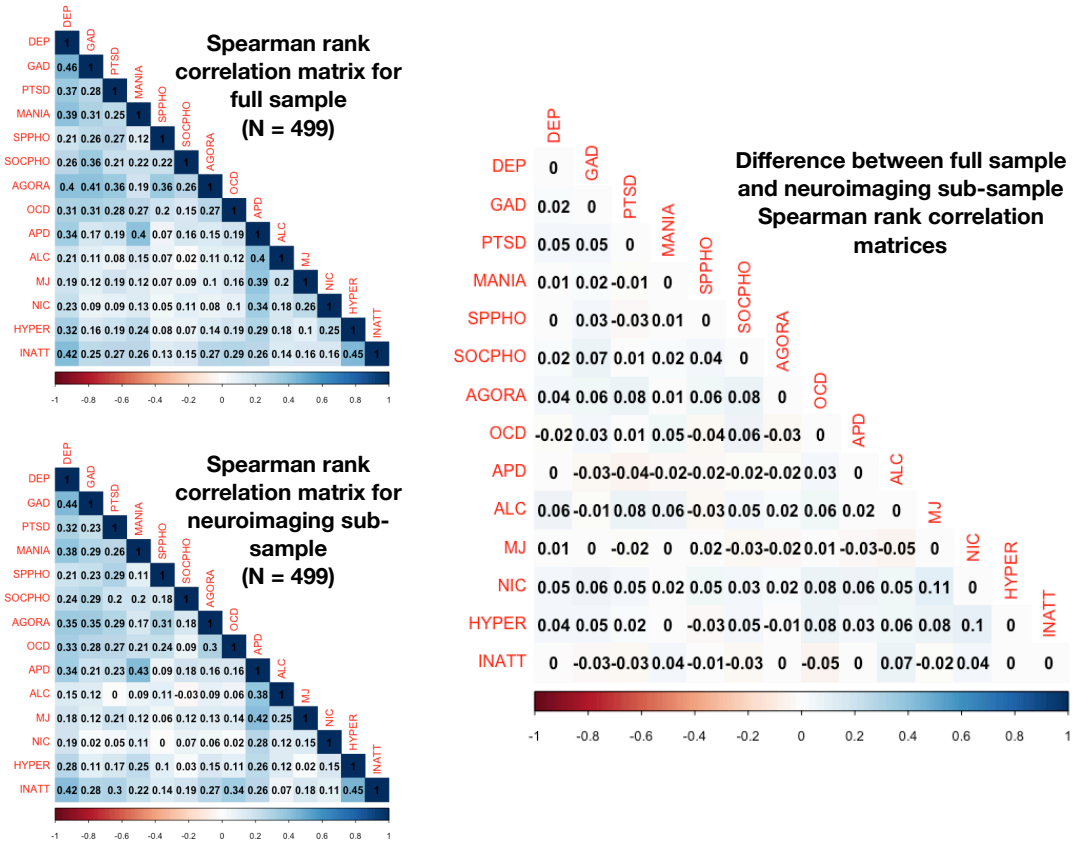

Figure 3.2: Differences between full sample and neuroimaging sub-sample correlation matrices. The top left figure illustrates the Spearman rank correlation matrix across symptom disorder dimensions for the full TTS Wave II sample ($N = 499$). The bottom left figure illustrates the Spearman rank correlation matrix across symptom disorder dimensions for the neuroimaging subsample (i.e., those who had valid neuroimaging data and passed QA; $N = 326$). The large figure on the right reflects the full sample correlation matrix minus the neuroimaging sub-sample correlation matrix. Positive values indicate that the correlation was larger in the full sample, while negative values indicate the correlation was larger in the neuroimaging sub-sample. DEP = major depressive episode, GAD = generalized anxiety, PTSD = post traumatic stress, MANIA = manic episode, SPPHO = specific phobia, SOCPHO = social phobia, AGORA = agoraphobia, OCD = obsessive-compulsive, APD = anti-social personality, ALC = alcohol use, MJ = marijuana use, NIC = nicotine use, HYPER = hyperactivity, INATT = inattention.

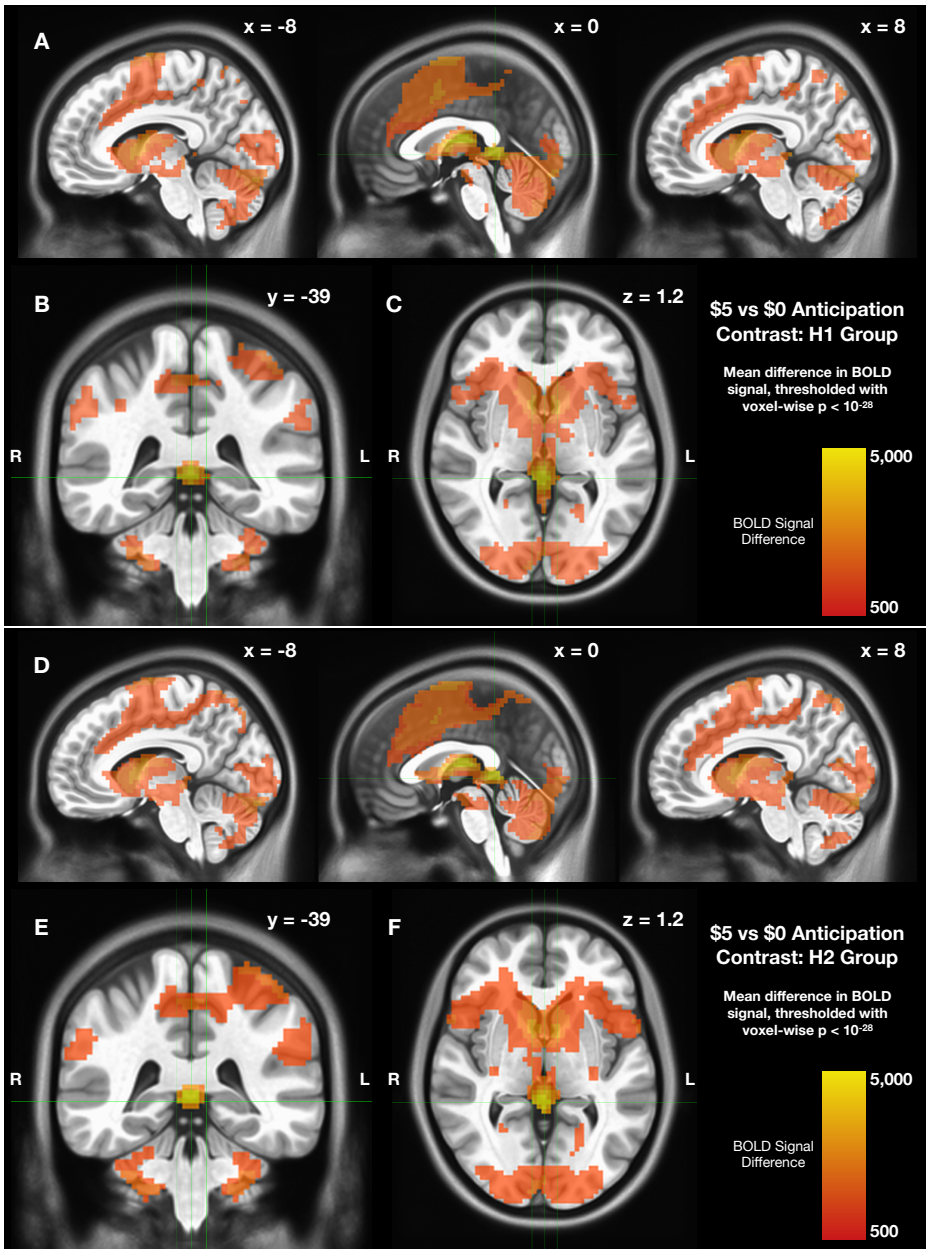

Figure 3.3: Thresholded maps showing outcomes from a split-sample analysis of the reward anticipation \$5 vs \$0 conditions contrast. Panels A, B, and C refer to the H1, while panels D, E, and F refer to H2. 3dttest++ mean difference estimate outputs were thresholded using AFNI by $p < 10^{-28}$, and overlaid onto the MNI 2009c Asymmetrical template brain anatomical image. All significant differences found were positive (i.e., higher BOLD activation in the \$5 anticipation condition than in the \$0 anticipation condition). Brighter (more yellow) colors indicate larger mean differences in β estimates. Images are centered at the peak MNI coordinates for the large cluster: $(x = 0, y = -39, z = 1.2)$. Panels A and D show sagittal views, where the center image is centered at $x = 0$, and the flanking left and right images are taken at $x = -8$ and $x = 8$, respectively, to illustrate activation and engagement of bilateral VS, VP, ACC, SMA, motor cortex, visual cortex, and cerebellum. L = left, R = right.

This indicates that, as expected, participants showed increased activation of the reward network, as well as other brain regions involved with preparing to make a quick response, when there was a high reward at stake, relative to no reward. One interesting thing to note, however, is that in both sub-samples the largest mean difference between the contrast maps was concentrated around a peak just under the splenium of the corpus callosum. This peak is hard to interpret and may be an artifact.

3.3.2 Reward attainment contrast

For the $5 condition hit vs. miss attainment contrast, I again found similar results across each half. Figure 3.4 shows activation maps thresholded at $p < .001$ and clustering with extent threshold $k = 34$. As expected, BOLD signal was significantly higher when participants learned they were successful and attained a $5 reward (hit; relative to when they learned they failed to attain this reward, or miss) in the VS and vmPFC. The vmPFC region showed the largest differences between hit and miss trials. In other regions, including the ACC and the pre-SMA, BOLD signal was significantly lower when participants learned they were successful and attained a $5 reward (hit; relative to when they learned they failed to attain this reward, or miss).

3.4 Unweighted CFA of full TTS Wave II sample

I did not complete model optimization steps since those were already described elsewhere (Lahey et al., 2018). The bi-factor model provided acceptable fit when not using weights (see Table 3.2 for a summary of fit statistics). Standardized factor loadings and residuals (Mplus STDYX) are illustrated in Figure 3.5 (note: line widths for each loading are proportional to the magnitude of that loading).

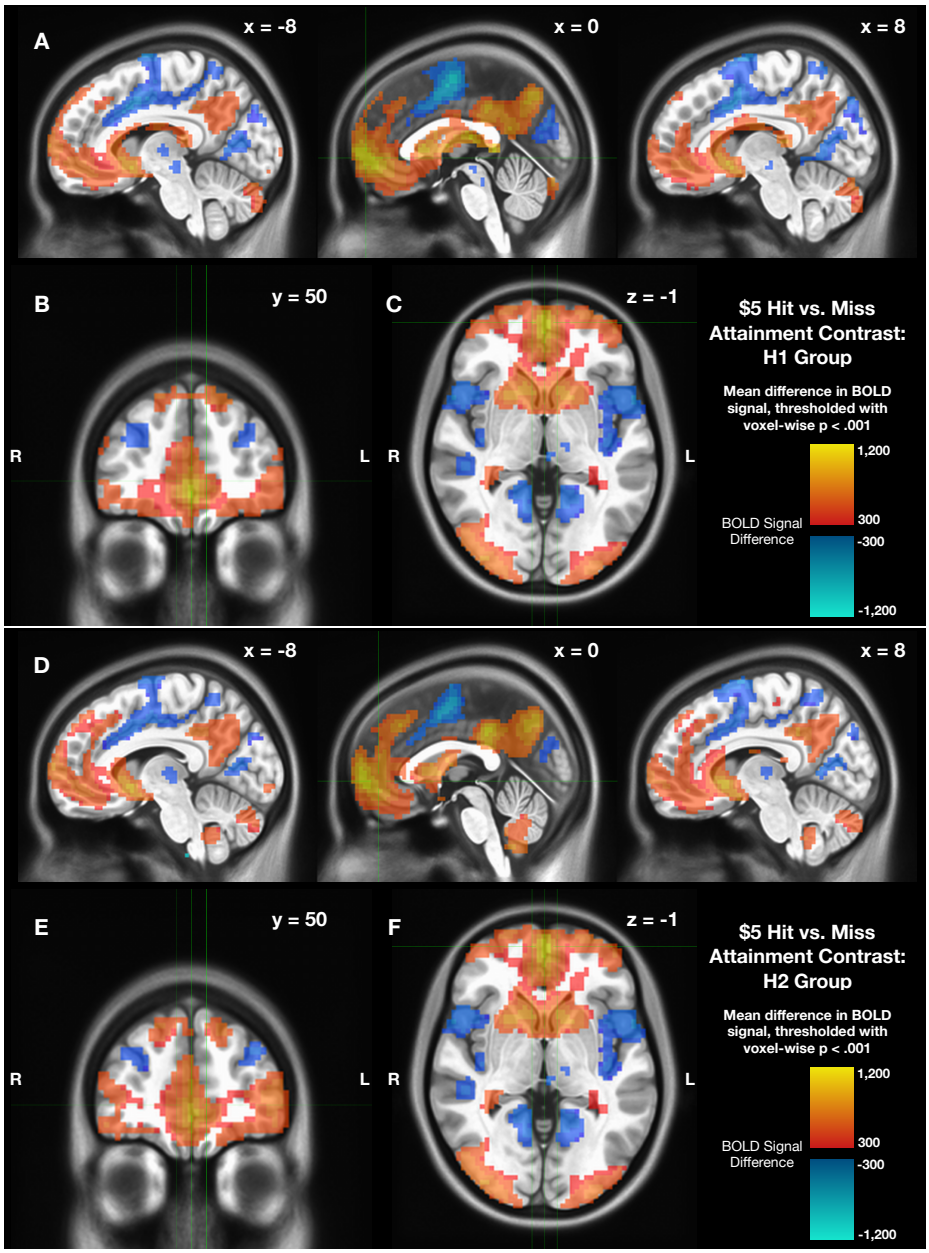

Figure 3.4: Thresholded maps showing outcomes from a split-sample analysis of the reward attainment contrast: hits vs. misses for the $5 trial condition. Panels A, B, and C refer to the H1, while panels D, E, and F refer to H2. 3dttest++ mean difference estimate outputs were thresholded using AFNI by $p < .001$, and overlaid onto the MNI 2009c Asymmetrical template brain anatomical image. Statistically significant differences coded in red indicate higher BOLD signal in the hit condition relative to miss; meanwhile, differences coded in blue indicate lower BOLD signal in the hit condition relative to miss. Brighter (more yellow or sky blue) colors indicate larger mean differences in BOLD signal. Images are centered at $(x = 0, y = 50, z = -1)$, close to the peak coordinates of vmPFC activation. Panels A and D show sagittal views, where the center image is centered at $x = 0$, and the flanking left and right images are taken at $x = -8$ and $x = 8$, respectively, to illustrate activation and engagement of bilateral VS and vmPFC. L = left, R = right.

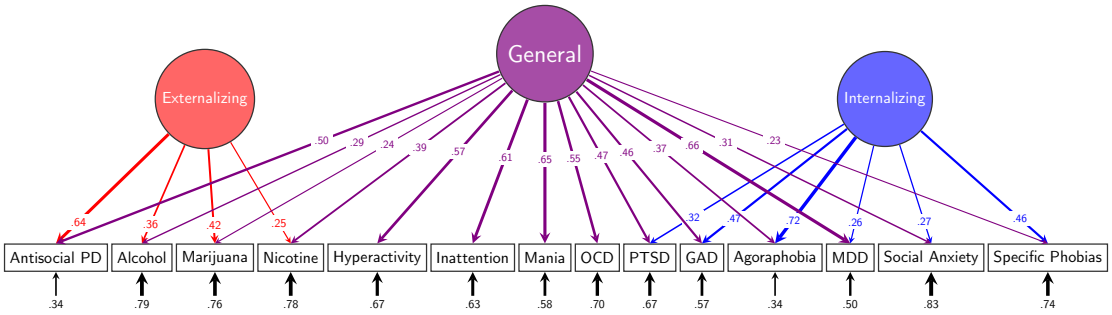

Figure 3.5: Confirmatory factor analysis of the full TTS Wave II sample ($N = 499$). All loadings and residuals are standardized (Mplus STDYX). Line widths for each loading are proportional to the magnitude of said loading. Manifest variables depicted above refer to symptom counts for each dimension, obtained from the YA-DISC clinical interview.

Fit statistic	Value
χ^2	114.79
df	67
p	.00003
CFI	0.946
TLI	0.927
RMSEA	0.038
90% CI	$0.026 - 0.049$
$p \leq .05$	0.959
SRMR	0.040
BIC	22369
AIC	22150

Table 3.2: Full sample unweighted CFA fit statistics. Note: df = degrees of freedom, CFI = confirmatory fit index, TLI = Tucker-Lewis index, RMSEA = root mean square error approximation, SRMR = standardized root mean square residual, BIC = Bayesian information criterion, AIC = Akaike information criterion.

3.5 Between subjects SEM: reward anticipation

3.5.1 General factor

One cluster survived multiplicity correction. This cluster, which primarily comprised the right SMA and a small section of the right ACC, indicated a statistically significant positive association between the reward anticipation contrast (BOLD activation in $5 minus $0 trials) and general factor scores (see Table 3.3 for full details).

I conducted a post-hoc analysis to assess whether task effects were present in this cluster. In order to do this, I defined a region of interest (ROI) mask based on the surviving voxels for this cluster, and I looked at its intersection with the thresholding masks for the manipulation check analyses with the two split samples. The outcome of this analysis is summarized in Table 3.4. For both H1 and H2, when using a voxel-wise threshold of $p < .001$, all 63 voxels in the cluster showed significantly greater BOLD activation in the $5 condition vs. the $0 condition. When looking at effect sizes and directionality, in H1, the average z value estimated by 3dttest++[2] for voxels in this cluster was 12.58, with z values associated with the paired t-test ranging from 7.21 through 13.00. Similarly, in H2, the average z value estimated by 3dttest++ for voxels in this cluster was 12.65, with z values associated with the paired t-test ranging from 6.87 through 13.00. In short, participants showed increased activation in this region in the $5 condition relative to the $0 condition regardless of their general factor scores.

3.5.2 Internalizing factor

Eight clusters survived multiplicity correction. These clusters comprised several brain regions, including right posterior cingulate cortex (PCC), right precuneus, right motor cortex, left pre-SMA, left cuneus, left middle frontal gyrus (MFG) in the dorsolateral pre-

[2] 3dttest++ transforms t-statistics estimated in the t-testing procedure into z values. Positive values reflect greater activation in the $5 condition relative to the $0 condition; negative values reflect greater activation in the $0 condition relative to the $5 condition.

Size (voxels)	Peak MNI coordinates	Estimated cluster α	Avg. effect size (Mplus STDYX)	Avg. SE (Mplus STDYX)	Anatomical regions
63	$(0, 18, 47)$	< 0.01	0.2370	0.0633	Right pre-SMA Right ACC

Table 3.3: Clusters surviving multiplicity correction for association between general psychopathology factor and reward anticipation MID contrast. Estimated cluster α is provided by AFNI, based simulations conducted with 3dClustSim (see Section 2.6.3).

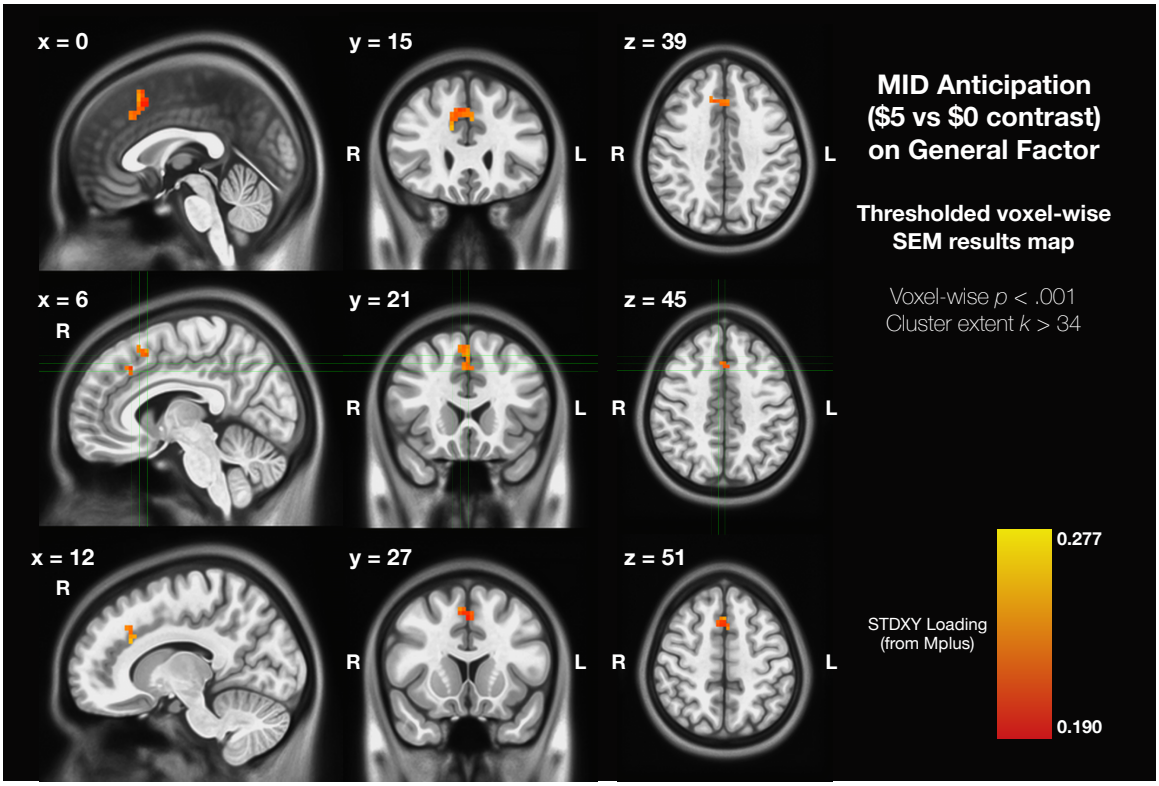

Figure 3.6: Thresholded maps showing outcomes from my voxel-wise SEM analysis, for the general factor $\rightarrow$ MID Contrast (z) path (see Figure 2.3). Path loading maps were thresholded using AFNI by using a voxel-wise $p < .001$ and a cluster extent correction factor of $k < 34$ (see Section 2.6.3), and overlaid onto the MNI 2009c Asymmetrical template brain anatomical image. The colored overlay represents a cluster of voxels in the brain for which the general factor to MID contrast path was statistically significant and survived thresholding; brighter (more yellow) colors indicate larger standardized (Mplus STDXY) path coefficients. All path coefficients were positive. L = left, R = right.

Cluster peak (voxels)	% voxels with $p < .001$	Mean z [range]
$(0, 18, 47)$		
H1	100.0	12.58 [7.21; 13.00]
H2	100.0	12.65 [6.87; 13.00]

Table 3.4: This table illustrates an examination of task effects in brain regions defined by the significant clusters identified in the voxel-wise SEM for internalizing factor. The second column indicates the percentage of voxels in the cluster mask that intersected with a mask of voxels that survived cluster correction at a $p < .001$ voxel-wise threshold in each pairwise t-test from the manipulation check. The third column indicates the average z-statistic associated with the t-test (see footnote) across all voxels in the region defined by this cluster, and the range of z values for all voxels within this region. All examinations were done in each half of the split sample (H1 and H2).

frontal cortex (dlPFC), left temporal pole. Additionally, two clusters emerged in the cerebellum, comprising both left and right areas IX and X, left area V, and the right crus II. In all these clusters, there was a statistically significant positive association between the reward anticipation contrast (BOLD activation in $5 minus $0 trials) and internalizing factor scores (see Table 3.5 for full details).

Using the same procedure as with the general factor cluster, I conducted a post-hoc analysis to assess whether task effects were present in these clusters. The outcome of this analysis is summarized in Table 3.6. At a $p < .001$ threshold, most clusters showed some degree of overlap across halves with voxels that had significant task effects after clusterizing and thresholding. Most of the voxels in the right motor cortex, the left pre-SMA, and the right crus II in the cerebellum showed significant task effects in the manipulation check ($>$90% across both halves); a majority of voxels in the left MFG, and bilateral areas IX and X and left area V of the cerebellum showed significant task effects in the manipulation check ($>$70% across both halves); more than half of voxels in the left cuneus showed significant task effects ($>$50% across both halves); while there was very little significant task effects in the right PCC and precuneous cluster areas (27.4% in H1, 15.8% in H2) and no significant task effects in the left temporal pole area cluster.

Size (voxels)	Peak MNI coordinates	Estimated cluster α	Avg. effect size (Mplus STDYX)	Avg. SE (Mplus STDYX)	Anatomical regions
143	$(-24,-39,-45)$	< 0.01	0.2719	0.6962	Cerebellum: bilateral areas IX, X; left area V
95	$(9,-54,21)$	< 0.01	0.2598	0.0684	Right PCC Right precuneus
52	$(-3,15,64)$	< 0.01	0.2549	0.0665	Left pre-SMA
45	$(-9,-69,14)$	< 0.02	0.2759	0.0695	Left cuneus
42	$(39,-78,-42)$	< 0.03	0.2497	0.0673	Cerebellum: right crus II
39	$(-51,3,44)$	< 0.04	0.2671	0.0690	Left MFG
38	$(-45,15,-22)$	< 0.04	0.2513	0.0635	Left temporal pole
36	$(15,-15,74)$	< 0.04	0.2984	0.0757	Right motor cortex

Table 3.5: Clusters surviving multiplicity correction for association between internalizing psychopathology factor and reward anticipation MID contrast. Estimated cluster α is provided by AFNI, based simulations conducted with 3dClustSim (see Section 2.6.3).

Cluster peak (voxels)	% voxels with $p < .001$	Mean z [range]
$(-24, -39, -45)$		
H1	79.7	6.46 $[-0.73; 13.00]$
H2	79.7	6.82 $[-1.78; 13.00]$
$(9, -54, 21)$		
H1	27.4	1.68 $[-2.64; 6.80]$
H2	15.8	0.26 $[-4.18; 5.56]$
$(-3, 15, 64)$		
H1	98.1	9.02 $[2.70; 13.00]$
H2	98.1	9.95 $[3.21; 13.00]$
$(-9, -69, 14)$		
H1	73.3	5.24 $[0.52; 13.00]$
H2	55.6	4.15 $[-1.77; 13.00]$
$(39, -78, -42)$		
H1	100.0	5.61 $[3.31; 6.87]$
H2	95.2	4.28 $[3.12; 5.74]$
$(-51, 3, 44)$		
H1	71.8	6.10 $[-3.28; 13.00]$
H2	74.4	7.18 $[-2.73; 13.00]$
$(-45, 15, -22)$		
H1	0.0	0.15 $[-2.97; 2.24]$
H2	0.0	-1.25 $[-3.29; 0.49]$
$(15, -15, 74)$		
H1	100.0	10.85 $[4.65; 13.00]$
H2	100.0	11.55 $[5.39; 13.00]$

Table 3.6: This table illustrates an examination of task effects in brain regions defined by the significant clusters identified in the voxel-wise SEM for internalizing factor. The second column indicates the percentage of voxels in the cluster mask that intersected with a mask of voxels that survived cluster correction at a $p < .001$ voxel-wise threshold in each pairwise t-test from the manipulation check. The third column indicates the average z-statistic associated with the t-test (see footnote) across all voxels in the region defined by this cluster, and the range of z values for all voxels within this region. All examinations were done in each half of the split sample (H1 and H2).

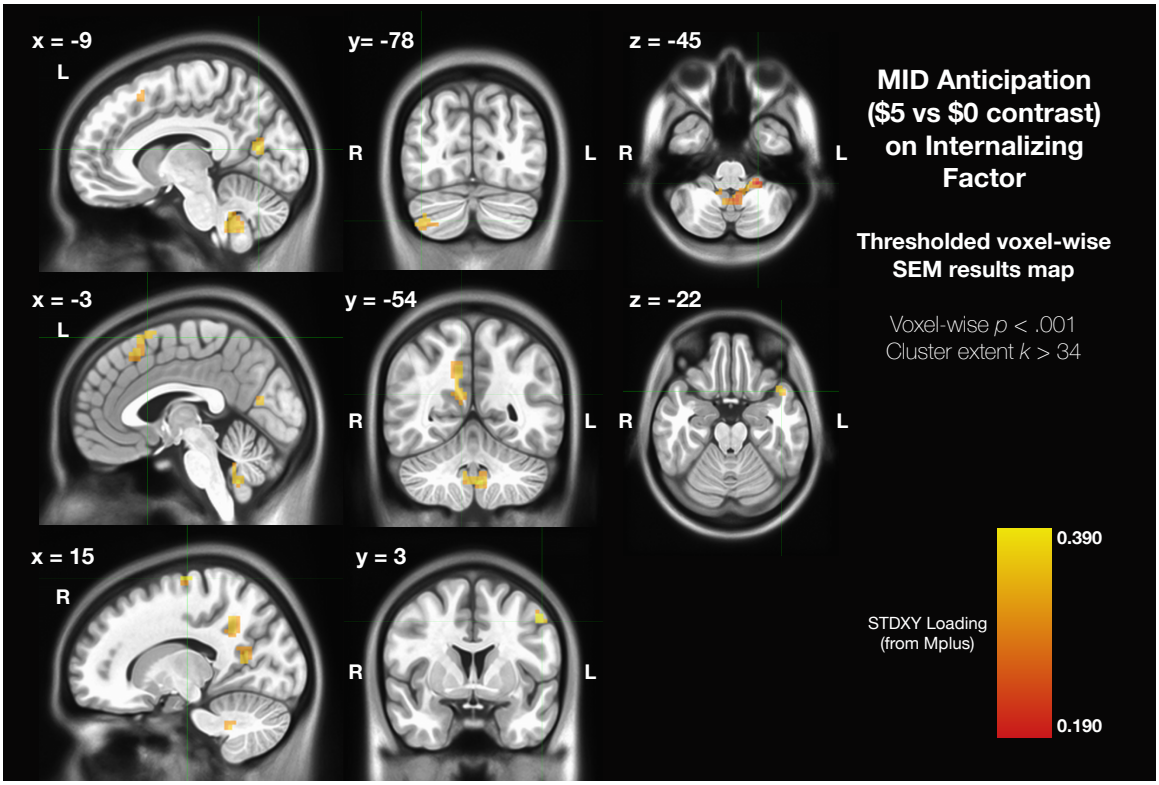

Figure 3.7: Thresholded maps showing outcomes from my voxel-wise SEM analysis, for the internalizing factor $\rightarrow$ MID Contrast (z) path (see Figure 2.3). Path loading maps were thresholded using AFNI by using a voxel-wise $p < .001$ and a cluster extent correction factor of $k < 34$ (see Section 2.6.3), and overlaid onto the MNI 2009c Asymmetrical template brain anatomical image. The colored overlay represents a cluster of voxels in the brain for which the internalizing factor to MID contrast path was statistically significant and survived thresholding; brighter (more yellow) colors indicate larger standardized (Mplus STDXY) path coefficients. All path coefficients were positive. All clusters are being shown at the same time across images; slices were chosen such that at least one slice is centered on the peak coordinates of one of the identified clusters. L = left, R = right.

3.5.3 Externalizing factor

No clusters survived multiplicity correction for the externalizing factor.

3.6 Between subjects SEM: reward attainment

No clusters survived our multiplicity correction for either general factor, internalizing factor or externalizing factor in relationship to the reward attainment contrast.

Chapter 4

Discussion

In this study, I sought to identify whether individual differences in higher-order latent psychopathology dimensions might be associated with activation in the reward anticipation and reward attainment contrasts for the MID task.

I tested the hypothesized that I would find associations between higher-order psychopathology and activation in the MID task contrasts across the brain. In more statistical terms, I hypothesized that in my SEM specification for each voxel the paths from the higher-order factors to the MID contrast would not be equal to 0. I expected that voxels for which these associations were significant would be largely localized to the reward network, although the path was tested for all voxels in the brain.

Consistent with my hypothesis, I found that there were significant associations between higher order factors of psychopathology (specifically general factor and internalizing factor) and the reward anticipation contrast of the MID task in some brain regions. Inconsistent with my hypothesis, I did not find any associations between the externalizing psychopathology factor and the reward anticipation contrast, or associations between any psychopathology factor and the reward attainment contrast.

In terms of localization of significant paths, the right dACC was the only brain region in the reward network that showed a significant association to higher-order psychopathology. The rest of the brain regions that showed significant associations with psychopathology factors are not traditionally associated with the reward network.

My results inform our understanding of the neural substrates of psychopathology by contributing to a growing body of evidence suggesting there are several differences in brain structure and function that can be ascribed to non-specific, dimensional transdiagnostic measures of psychopathology. Specifically, the present study expands on the initial

findings by Shanmugan et al. (2016) that higher-order psychopathology dimensions are associated with differences in brain activation in an *n*-back fMRI task paradigm, by showing that higher-order psychopathology is also associated with activation in a different task paradigm, the MID task. More broadly, the present study contributes to ongoing efforts to identify neural substrates that might non-specifically contribute to several forms of psychopathology and their co-morbidity. These efforts may, in the future, help with narrowing down the extent to which brain differences may confer broad vulnerabilities or more specific vulnerabilities to sets of symptoms, which is not a question that can be directly tackled in case-controlled designs.

In terms of the relationship between reward and psychopathology, my findings suggest that higher-order psychopathology effects on reward processing are limited to reward anticipation, and not the reward attainment stage. Keeping in mind several prior case-controlled studies that found associations between disorders and reward attainment, one possible reason why no associations were identified between higher-order psychopathology and reward attainment may be that brain mechanisms operating at this level might be more specific to certain symptom dimensions or disorders. This would also be to some degree consistent with the existing contradictions across findings for various disorders. This explanation could be further explored in a case-controlled re-analysis of the TTS Wave II dataset, or in further studies.

4.1 Reward anticipation contrast associations to higher order psychopathology

The reward anticipation contrast of the MID task contrasted BOLD response when participants were preparing to make a response in a trial where a $5 monetary reward was at stake to BOLD response when participants were preparing to make a response in a trial where no monetary reward was at stake. As evidenced by our manipulation check (see Section 3.3.1), this contrast robustly reflects how higher reward trials recruited the entire reward network more than no reward trials, increasing blood flow to almost all key regions

in the reward circuit including the bilateral VS, VP and ACC. The task effects evident in this contrast are highly consistent with what was expected by prior literature on the MID task (see Section 1.4.1).

4.1.1 General psychopathology factor

In my voxel-wise SEM analyses, the general psychopathology factor showed a positive, statistically significant, association with a cluster of voxels comprising right pre-SMA and right dorsal ACC. This suggests that higher general psychopathology was associated with increased activation of right pre-SMA and dACC when preparing to make a response in high reward trials, relative to no reward trials.[1] Subsequent analyses also revealed that in the area demarcated by this cluster, there was also a significant positive effect of task, where practically all voxels showed greater activation in the $5 trials relative to the $0 trials.

Right dorsal ACC. Consistent with my hypothesis, a small section of the right dorsal ACC (part of the reward network) was included in this cluster of voxels associated with the general factor. Looking at the case-controlled study literature, this finding is consistent with meta-analyses of fMRI data suggesting elevated activation of the ACC across major depressive disorder (W. N. Zhang et al., 2013; Hamilton et al., 2012) and anxiety disorders (Etkin & Wager, 2007); and furthermore, this finding is also consistent with the cross-disorder meta-analysis by Goodkind et al. (2015), which identified grey matter loss in the dorsal ACC across patients with schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety. Functional differences in right ACC response have also been previously linked to general psychopathology in the PNC studies. Kaczkurkin et al. (2017) found that higher general psychopathology was associated with *increased* perfusion to the right dorsal and left rostral ACC while at rest using rCBF techniques, while Shanmugan et al. (2016) found that higher general psychopathology was

[1] Because these findings are from data collected in the same wave, I would refrain from making any causal inferences here.

associated with *decreased* activation in the 2-back > 0-back contrast of the *n*-back task.

It is important to note that the dorsal ACC does not just play a role in reward processing; in fact, the ACC is effect in numerous other processes such as performance monitoring (Carter & Van Veen, 2007) and affect regulation (Bush, Luu, & Posner, 2000). Given the breadth of processes the ACC is involved in, it is important to point out that the association identified between the general factor and the reward anticipation contrast might not necessarily emerge exclusively during reward anticipation, but rather might also emerge during other non-reward related psychological processes as well. That said, because the ACC is involved in so many processes, any kind of dysfunction in the ACC might confer vulnerability to a variety of psychiatric symptoms, which would be consistent with the association identified between ACC and general factor.

Right pre-SMA. Along with right dorsal ACC, the cluster of voxels associated with the general factor included a section of right pre-SMA. The pre-SMA is commonly thought of in relation to a cognitive control network, which also incldues the inferior frontal gyrus (IFG) and some regions of the basal ganglia like the subthalamic nucleus (STN) (Aron, Behrens, Smith, Frank, & Poldrack, 2007). The pre-SMA is considered to be an essential node in this network, supporting cognitive control of actions that require rapid updating, inhibition, or switching (Obeso, Robles, Muñoz-Marrón, & Redolar-Ripoll, 2013). I did not initially hypothesize that there would be a significant relationship between general factor and the reward anticipation contrast for pre-SMA, and there are multiple possible interpretations for this finding. One such possible interpretation relies on previous work by (Forstmann et al., 2008), which suggests that right pre-SMA is activated when participants are preparing to make responses under time pressure.[2] In the MID anticipation phase, participants are essentially preparing to making a quick response under time pressure (when

[2]In their study, Forstmann and colleagues had participants complete a moving dots task in the scanner, in which participants had to ascertain the direction in which a cloud of dots were moving. Prior to each trial, participants were given a cue of whether they should respond emphasizing speed, accuracy, or neutral. The authors found increased activation in right pre-SMA and right striatum for the cue speed > neutral fMRI contrast (Forstmann et al., 2008).

the target appears), and they are especially motivated to provide a quick response in the $5 reward trials since there is actual money at stake. If we refer back to the "reward facilitation" conceptualization offered by Zald and Treadway (2017) (presented earlier in Section 1.3), the reward anticipation phase contrast does not just reflect motivational differences, but also it shows how multiple perceptual, attentional, cognitive and motor processes are engaged in preparation to make a response when a reward is at stake. One might thus postulate that, perhaps, task effects reflecting increased engagement of pre-SMA in the $5 relative to the $0 condition are due to increased preparation to make a quick response for these trials under time pressure; and in this vein, participants with higher general psychopathology needed to activate their right pre-SMA more than those with lower general psychopathology to achieve the same desired outcome. That said, this is one of many possible interpretations, and further work needs to be done in order to further understand the meaning and implications of links between pre-SMA and general psychopathology.

4.1.2 Internalizing psychopathology factor

In my voxel-wise SEM analyses, the internalizing psychopathology factor showed a positive, statistically significant, association with eight clusters of voxels, comprising a wide array of brain regions: left pre-SMA, left cuneus, left MFG (dlPFC), left temporal pole, right PCC, right precuneus, right motor cortex, and cerebellum. This would suggest that higher internalizing psychopathology scores were associated with increased activation of the aforementioned brain regions when preparing to make a response in high reward trials, relative to no reward trials. The brain regions identified to show significant associations to internalizing psychopathology in this analysis do not clearly belong to a single network or circuit, nor are they associated with the core reward circuit regions. Furthermore, for some of these regions it is not entirely straightforward why they might be associated with internalizing psychopathology.

An important preamble to this discussion is to keep in mind that the internalizing factor,

as defined in my bi-factor model specification, is not the "same" as other conceptualizations of internalizing from correlated factor models. That is, while in a correlated factors model the internalizing factor models covariance across all internalizing disorders, in a bi-factor model the internalizing factor is modeling the covariance among internalizing disorders that is not explained by the general factor. Thus, my use of "internalizing factor" here differs from that that has been used in prior papers.

Left pre-SMA. It is interesting that left pre-SMA emerged as significantly associated with the internalizing factor, especially considering how right pre-SMA was associated with the general factor. Just like the right pre-SMA cluster discussed above, the left pre-SMA associated with internalizing factor showed significant task effects (i.e., it across participants it was activated more strongly in the $5 condition than the $0 condition). One possible explanation for this is that, just as it was proposed for the right pre-SMA association with general factor, individuals with higher disposition to develop internalizing psychopathology might engage left pre-SMA more in order to prepare themselves for a fast motivated response. The lateralization aspect of this association is also interesting; perhaps, it is possible that differential engagement in left pre-SMA might be specific to the internalizing dimension, while differential engagement in right pre-SMA might be common across all symptom dimensions. All these hypotheses and potential interpretations are not, however, the only possibilities, and would require support from further studies in order to be taken seriously.

Right PCC and right precuneus. The posterior cingulate and the medial precuneus have been consistently associated with correct remembering of previously learned items, including autobiographical memories (Maddock, Garrett, & Buonocore, 2001; Vincent et al., 2006). Some evidence also exists that the PCC may help mediate interactions of emotional and memory-related processes (Maddock, Garrett, & Buonocore, 2003). The PCC/precuneus regions are generally thought about within the context of the default mode network in the brain (DMN). The DMN has been traditionally conceptualizing as involving three

major subdivisions: the ventromedial prefrontal cortex (vmPFC), the dorsal medial prefrontal cortex (dmPFC) and the PCC/precuneus. Broadly, the DMN is believed to play playing a role in processes that support emotional processing, self-referential mental activity, and recollection of prior experiences, with the PCC/precuneus being particularly associated to this latter function (Raichle, 2015). Brain activation in DMN regions, including the PCC/precuneus, are greater at rest than during engagement in goal directed-tasks across multiple modalities, a phenomenon that has been coined "task deactivation" or "task suppression" of the DMN (see Whitfield-Gabrieli (2017) for a full list of references). Interestingly, studies have shown task suppression of the DMN is reduced in patients with major depressive disorder in tasks of emotion perception and judgment (Grimm et al., 2009) and during passive viewing and reappraisal of negative pictures (Sheline et al., 2009). Considering this line of research, one possible interpretation of the observed effect is that the observed cluster reflects participants with higher internalizing scores tended to exhibit less task suppression in the PCC/precuneus region of the DMN.

Left temporal pole. The temporal pole is understood functionally as a paralimbic region, and has been associated with face processing, emotional processing of sensory stimuli, and theory of mind across several neuroimaging studies (Olson, Plotzker, & Ezzyat, 2007). The specific reason why this region might have shown a positive association with the reward anticipation of the MID task remains unclear. It is interesting to note that, as stated in Table 3.6, this region did not show any task effects (i.e., it across participants it was not engaged more in the $5 condition than the $0 condition). Taking this into consideration, one potential interpretation for this effect is that perhaps the temporal pole was engaged more throughout the task for individuals with higher internalizing scores due to anxiety related to scanning processes, unrelated to the task itself.

Right motor cortex. It is unclear why engagement the right motor cortex may have been associated with internalizing psychopathology in this task. One possibility is that participants with higher internalizing scores tended to fidget or move more the left side of their

body during the scanning process, due to increased anxiety or discomfort. However, this proposed explanation is a bit of a stretch given that if participants were fidgeting around, I would have expected a bilateral relationship between internalizing and motor cortex.

Cerebellum. Although the cerebellum was traditionally thought of as exclusively contributing to the planning and execution of movement, mounting evidence from neuroimaging studies, neuroanatomy studies and lesion studies has supported the view that the cerebellum also serves several non-motor functions (Buckner, 2013). Cerebellar activation has been associated with a broad array of tasks, including those used to assess attention, executive control, language, working memory, learning, pain, emotion, and addiction (for a full list of references, see Strick, Dum, and Fiez (2009)). Anatomical and functional differences in cerebellum have also been associated with a wide spectrum of disorders, including ADHD, autism spectrum disorders, schizophrenia, bipolar disorder, major depressive disorder, and anxiety disorders (Phillips, Hewedi, Eissa, & Moustafa, 2015; Moreno-Rius, 2018). The human cerebellum is not a monolithic brain region: it has a distinct functional topography (Stoodley & Schmahmann, 2009; Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011; Stoodley, Valera, & Schmahmann, 2012). For this reason, it is important to focus discussion on specific areas of the cerebellum that are of interest.

Cerebellum: bilateral area IX. As pointed out by Habas et al. (2009), area IX of the cerebellum has been implicated in various functional tasks including thirst satiation (Parsons et al., 2000), sensation (Hui et al., 2005), motor synchronization (Jantzen, Steinberg, & Kelso, 2004), working memory (Desmond, Gabrieli, Wagner, Ginier, & Glover, 1997), and perception of change in stimulus timing (T. Liu, Xu, Ashe, & Bushara, 2008). Keeping in mind that a significant cluster associated with internalizing psychopathology also emerged in the PCC and precuneus, it is interesting to note that Area IX, along with retrosplenial and precuneus cortex, have been implicated in past and future event elaboration (Addis, Wong, & Schacter, 2007). Furthermore, at least three resting-state studies have suggested that area IX shows strong connections to the default mode network (DMN)

(Habas et al., 2009; Filippini et al., 2009; Buckner et al., 2011), which also includes the PCC and precuneus, and has been implicated in several psychopathological processes including rumination (Broyd et al., 2009; Whitfield-Gabrieli, 2017).

Cerebellum: bilateral area X. Area X of the cerebellum, also referred to as the flocculonodular lobe or vestibocerebellum, receives substantial input from the vestibular nerve, and serves as a regulator of the vestibular system (Haines & Mihailoff, 2018). I was unable to find any references connecting this area with pscyhopathology, so it is difficult to come up with a good interpretation for what this relationship might mean. It is also possible that, because areas IX and X are close together, involvement of area X may be an artifact from blurring.

Cerebellum: right crus II (area VII). The crus II is a subdivision of area VII of the cerebellum. A meta-analysis of fMRI studies found associations between the right crus II and activations in language related tasks (Stoodley & Schmahmann, 2009); a follow-up fMRI study also found the right crus II region showed peaks during mental rotation tasks (Stoodley et al., 2012). A functional connectivity also found the bilateral crus I and II contributed to the right and left executive control networks (Habas et al., 2009). Buckner et al. (2011) also found that the crus II showed functional connectivity with the default mode network (DMN), which is interesting in light of the other significant cluster in the PCC/precuneus.

Cerebellum: left area V. Area V of the cerebellum has anatomical been implicated in a closed-loop circuit between cerebellum and motor cortex in a virus transport study of non-human primates (Kelly & Strick, 2003), and has previously been associated with right finger tapping in the scanner in a prior study (Stoodley et al., 2012). Involvement of left area V is interesting in light of the other significant cluster that emerged in the right motor cortex, with which this region is anatomically linked. Just like the finding for right motor cortex, however, it is difficult to make sense of why this area of cerebellum would be associated with the internalizing factor. It is important to note however, that there is a very

small portion of area V in the significant cluster identified, so it is possible that the small number of voxels showing a significant relationship in this area may be just an artifact that emerged from smoothing the images.

Left cuneus. The cuneus, located in the occipital lobe, is involved in processing of visual information (Wandell, Dumoulin, & Brewer, 2009). Its association with the internalizing factor here is difficult to interpret.

Left MFG (dlPFC). The dorsolateral prefrontal cortex is typically associated with executive functions, including working memory and selective attention. The dlPFC is considered to be a primary node in dorsal attentional networks that are linked to basic cognitive selection of sensory information and responses (Sturm, Haase, & Levenson, 2016). The dlPFC neurons are also sensitive to various aspects of reward, including quantity, quality, availability and delay of rewards (Kobayashi, 2009). In terms of our finding, there are several possibilities why internalizing might have been related to dlPFC in the MID anticipation contrast. One possibility is that individuals with higher internalizing disposition needed to engage dlPFC more than those with lower internalizing disposition, in order to maintain their attention and focus on the task and prepare to make a quick response. Another possibility is that individuals with higher internalizing disposition were more sensitive to the quantity of reward, such that their dlPFC was activated more than in those with lower internalizing disposition because they responded more strongly to the higher reward.

4.1.3 Themes

Taking all these findings into consideration, one might thus propose a few themes for the observed pattern of associations. The first theme relates to the pre-SMA: it is interesting that left pre-SMA activation was positively associated with internalizing, while right pre-SMA activation was positively associated with general psychopathology. One proposed explanation for pre-SMA involvement suggests that individuals high in internalizing and general psychopathology might need to engage their pre-SMA more in order to prepare

themselves to make responses under time constraints, although this is purely speculative and would require further testing. A second theme pertains to DMN: the right PCC/precuneus and the right crus II and bilateral areas IX in the cerebellum, which were all positively associated with internalizing psychopathology factor scores, are also all part of the DMN. Given the direction of the finding, one proposed explanation (out of many possible explanations) is that higher internalizing psychopathology scores might be associated with reduced task suppression. That is, activation in DMN regions in the task is positively associated with internalizing factor scores because individuals with higher internalizing psychopathology had more difficulty suppressing DMN than those with lower internalizing psychopathology. Again, this proposed explanation is speculative and would require further testing and consideration. A third theme could be engagement of motor regions, which is illustrated by the clusters in the right motor cortex and left area V / bilateral area X of the cerebellum. One might think this is associated with increased motor agitation while in the scanner, although this harder to interpret given the laterality of these clusters.

4.1.4 Notable absences.

Perhaps the most surprising absence here is the lack of any kind of pattern of association with basal ganglia structures, particularly the VS. Differential response to reward anticipation in the VS has been associated with a mulititude of disorders, albeit in different directions: ADHD (decreased activation) (Plichta & Scheres, 2014), addiction (decreased activation) (Balodis & Potenza, 2015), Bipolar I (increased activation) (Nusslock et al., 2012), externalizing disorders in adolescence (increased activation) (Bjork et al., 2010), schizophrenia (decreased activation) (Juckel et al., 2006). It is possible that these divergences in directionality and the lack of findings here might be due to VS differences in response to reward anticipation corresponding to more dimension-specific mechanisms. This might be tested with our data by, for example, re-analyzing the data using a case-controlled approach.

4.2 Reward attainment contrast (lack of) associations to higher order psychopathology

It is particularly interesting to note that no significant associations were found between the reward attainment contrast and higher-order psychopathology dimensions, especially since the manipulation check (Section 3.4) appears to suggest the reward anticipation contrast engaged the reward network and looked like what I would have expected from the previous literature. Again, the biggest missing piece here is the striatum, which has been implicated in several studies discussed earlier, e.g. for MDD (decreased activation) (Pizzagalli et al., 2009), for bipolar I disorder (increased activation) (Dutra et al., 2015), and in a meta-analysis of addicted populations (increased activation) (Luijten et al., 2017). Again, it is possible that the lack of findings in striatum might reflect that psychopathology related effects on this region are better understood as dimension-specific.

4.3 Strengths and weaknesses of the chosen methodological approach for between-subjects analyses

4.3.1 Strengths

The voxel-based SEM approach I chose has several strengths.

First, by using Mplus to conduct my neuroimaging analyses, I am able to appropriately handle several aspects of the complex design of the TTS Wave II sample. Sampling issues have been partially (though not fully) addressed, by accounting for sampling strata in the Mplus model specification. Non-independence has also been addressed in the same way my group's past epidemiological analyses have, by clustering twin pairs in Mplus (Lahey et al., 2018); according to the Mplus manual, this allows for proper adjustment of standard error estimates (L. Muthén & Muthén, 1998-2017).

Second, by using SEM this approach also allowed me to directly test relationships between the latent higher-order factor variables and neural response, without having to rely on factor score estimates.

Third, the decision to fix loadings based on the CFA of the full sample allows us to ensure that the model coefficient estimation is not biased by the sub-sample or voxel-specific issues[3], and is consistent with past studies from our group (Hinton et al., 2019).

Fourth, this approach allowed us to conduct a brain-wide voxel-wise analysis, allowing us to identify areas that we might not have *a priori* expected to show associations with these factors while still correcting for multiplicity effects.

Fifth, by limiting the SEM analysis to only the 326 subjects with neuroimaging data, I did not have to exclude covariates due to missing data. Data for handedness and scanner is missing for some participants[4], and Mplus refused to admit missing data for exogenous manifest variables in the SEM, which may have required me to exclude said covariates from the analyses.

Finally, this approach overcomes the limitations of existing software and has the potential to yield a new methodological approach as well as a use case for the literature.

4.3.2 Weaknesses

However, this approach has several weaknesses that must be acknowledged.

First, my approach did not fully account for sampling issues such as the probability of selection into Wave II and non-response.[5] This is important because the path coefficients and associated standard errors in my approach may be biased with respect to the representative TTS Wave I due to biased sampling (both from Wave II and the neuroimaging QA). Furthermore, because other analyses published by our group used the weights to account for these sampling issues, my analyses are inconsistent in this regard with past work by my group.

[3] I am thankful to Dr. Tomarken for pointing this out to me in our discussions.

[4] Handedness is missing for 16 out of 499 subjects in the full sample, and a scanner assignment was not made for 51 out of 499 participants.

[5] Although it would have been ideal to generate these weights for our specific sub-sample, weighting issues for the TTS Wave II project have been handled by our collaborator Paul Rathouz, who was not able to send us a set of weights for the fMRI subsample or the code to generate said weights by the time I needed them for my master's thesis analyses.

Second, by fixing factor loadings in the SEM, I made it difficult to accurately assess model fit for each of the SEMs.[6] Degrees of freedom are inflated due to fixing all the loadings in the measurement model.

Third, by only including 326 participants with fMRI data in the SEM, I am reducing the amount of information that can be used in the SEM to estimate latent psychopathology dimension scores; it is possible that, if I had included all 499 participants in Wave II, I would have obtained a different result. One way I think about this is in terms of a missing data problem. I have $N = 499$ participants with full psychopathology data, I am missing data for some important covariates for some participants that did not complete scanning ($N = 16$ for handedness, $N = 51$ for scanner) and I am either excluding or missing neuroimaging data for $N = 173$ participants. My approach was essentially performing a list-wise deletion of all the $N = 173$ participants who either were missing and/or did not pass QA (which also addressed the missing data problem for the covariates), and then fixing the loadings in the measurement model to those obtained in the $N = 499$ sample to avoid biases in those loadings. It is possible that my list-wise deletion approach to the missing data problem here led to biases in my estimates, and that more sophisticated approaches to dealing with missing data may have provided more accurate parameter estimates.

Fourth, the spatial multiplicity correction approach being used has not been validated empirically for used in a voxel-wise SEM context, and it could not be used in higher voxel-wise uncorrected p-thresholds (i.e., $> .002$) because at those thresholds it is prone to very high false positive rates. This limitation prevented me from examining regional effects that may have been smaller in magnitude but perhaps more diffuse across brain regions.

Finally, another important limitation with the chosen between-subjects analysis approach is that I used contrast coefficients as outcome variables. By doing this, I am essentially failing to account for the within-subject variance embedded in that contrast, which could bias my effects. Ideally, I would have preferred to model these effects as interactions

[6] Again, I am thankful to Dr. Tomarken for pointing this out to me in our discussions.

between higher-order psychopathology and MID condition, since this would also include modeling of the within-subject variance. However, I did not have the technical sophistication necessary to come up with a way of achieving this analysis while appropriately accounting for the complexity of this sample.

4.4 Limitations

Beyond the aforementioned limitations to the chosen between-subjects approach, there are several other limitations to this study that I would like to point out.

First and foremost, it is important to acknowledge that the use of a bi-factor approach to model dimensions of psychopathology is not without its controversy. As articulated by Bonifay et al. (2017), bi-factor models raise issues of interpretability, model fit, and vaidation. First, interpreting internalizing and externalizing factors that are orthogonal to the general factor is challenging because they need to be conceptualized as sub-constructs exclusive from the general factor. This interpretation is very different than the traditional understanding of internalizing and externalizing seen in the literature for correlated factor models, which are constructs that have important overlap with the general factor. Second, it is difficult to assess model fit for the general factor (Bonifay et al., 2017; Markon, 2018), since statistical fit indices can be biased in favor of the bi-factor model, even if the true population model follows a different structure (Murray & Johnson, 2013). Indeed, quantitative studies have shown that bi-factor models tend to over-fit the data (Bonifay & Cai, 2017) and accommodate nonsense response patterns (Reise, Kim, Mansolf, & Widaman, 2016). Third, the bi-factor model construct needs to be validated beyond tests of model fit (Bonifay et al., 2017).

The aforementioned challenges are all relevant to our study. The interpretability and clinical translatability of our findings for the residualized internalizing factor are complicated by the fact that the nature of this factor is somewhat hard to interpret. Our model fit statistics for the bi-factor model were not particularly great, and it is not fully clear whether

less biased model fit indicators might suggest that the bi-factor approach was not acceptable. It is also concerning that for our sample, correlated factor models tended to provide poor fit, with the highest CFI/TLI obtained being .811/.768 (Lahey et al., 2018). Finally, the validity question is also important. In a sense, this concern has been addressed to a greater degree in recent years, with the publication of a large number of studies supporting the criterion validity of a general factor approach (reviewed in Section 1.1) and the publication of several other studies identifying neurobiologiocal correlates for the general factor (e.g., Shanmugan et al. (2016); Snyder et al. (2017); Kaczkurkin et al. (2017); Romer et al. (2018); Hinton et al. (2019)). However, concerns still remain about the validity of the general factor. The effect sizes identified in many of these imaging studies were small (although this is also the case for many case-controlled designs; see Paulus and Thompson (2019)). And furthermore, in a recent pre-print Watts, Poore, and Waldman (2019) found that bi-factor models tended not to explain additional variance in first-order psychopathology symptom dimensions or external criteria (albeit with a measure that is not at present well-validated).

An additional important limitation as it pertains to our specification of the general factor is that it lacks any representation for individuals with psychotic disorders. Very few studies so far have included psychosis in its factor specification, so the exact relation of psychosis to the general factor is still unclear. It is also unclear how including psychosis in the measurement model might change the nature of the general factor construct itself.

Another important source of limitations in our study pertains neuroimaging. Neuroimaging studies have several "experimental degrees of freedom", in that there are multiple decisions that are made in the choices for how to pre-process and analyze the data that can significantly impact outcomes of the analysis. I tried to inform many of my decisions for how to do the analysis for this study based on the available empirical evidence from the neuroimaging literature, although it must be noted that there are several steps for which there is no singular best way to go about things. It is possible that I would have

obtained different results if I had used a different pre-processing, quality assurance, or within-subjects analysis modeling approach, even keeping the between-subjects modeling approach the same. Testing out different methods was complicated because of the immense amount of computational power and storage required for these analyses[7] and the size of the TTS sample.

Even if my chosen analysis approach and pipeline were optimal, I may have missed some outliers in my quality assurance that could have influenced results. Although I found the automated ART pipeline to be effective at detecting and flagging problems such as excessive motion and signal dropout, it is possible ART might have missed some regional artifacts, or that there were other problems in pre-processing that were missed by research assistants in their manual review of the data.[8] Particularly concerning in this note is the peak just under the splenium of the corpus callosum observed for the anticipation $5 - $0 contrast, which is really hard to interpret.

4.5 Future directions

There are several future directions to explore following this study.

The findings in this study require a significant amount of further work in order to be more robustly characterized. It might be helpful to leverage large datasets being collected with data on the MID task, like ABCD, to determine whether these findings are reproduced/generalizable or whether they are idiosyncratic to this sample. If these findings indeed are replicated on other samples, it might be worth doing some more work to try to understand the nature and implications of said findings. For example, for the pre-SMA findings, it would be valuable to examine a large population on a task that is more focused on varying speed constraints, like the one used by (Forstmann et al., 2008), and testing whether high general factor scores are associated with pre-SMA activation when making

[7] In preparing for this thesis, I became the ninth heaviest user of the ACCRE computational cluster at Vanderbilt. I'm sorry, David.

[8] Which is understandable - it is very tedious to review manually over 430 subjects with 3 runs!

responses under time pressure, but not associated with pre-SMA activation when making responses under no time pressure. Meanwhile, the DMN task suppression hypothesis might be tested by examining whether clusters like these emerge in the two other tasks participants in the TTS Wave II sample completed, and coupling this with an additional study that included resting state data and a task more directly designed to test for DMN suppression.

It might also be interesting to repeat our analyses using an ROI approach focused on the key reward network regions discussed earlier (see Section 1.4). It is possible that there were some significant, but subtle, effects in rewards regions that did not survive voxel-wise thresholding due to the high p-threshold, which might be identifiable using an ROI approach.

It would also be valuable to re-analyze this dataset using a case-controlled approach; i.e., to test for differences between TTS Wave II participants who qualified for each disorder and those who did not qualify for any disorders, for every disorder. This type of analysis would be informative, although one might also want to think carefully about how to account for all these analyses.

In terms of defining the latent variables, it would be interesting to see whether the TTS Wave II would conform with a hierarchical model (i.e., with a second order general factor that loads onto internalizing and externalizing), and if so, how the relationships with brain response would change. As pointed out by Markon (2018), the hierarchical model is a special case of the bi-factor model, which conceptually frames internalizing and externalizing factors as "mediators" of general factor influence. This model is perhaps more directly conforming with the causal hierarchical taxonomy hypotheses postulated by Lahey et al. (2017), wherein etiological influences go from less to more specific. Another interesting variation might involve attempting to estimate higher-order psychopathology from an item level, as opposed to a symptom dimension level.

Although our analyses here are correlational in nature, it would be interesting to explore causality by examining whether Wave I higher-order psychopathology predicts differential

brain response in the MID contrasts for Wave II. This would provide a more direct test of the causality hypothesis postulated by Lahey et al. (2017).

In terms of neuroimaging, it would also be interesting to assess whether the same results are obtained if some methodological aspects of the analyses are changed (e.g., using a different pre-processing pipeline, or estimating within-subject parameter maps and contrasts using another software like SPM12). This would speak to some degree to how reproducible our findings might be.

It would also be interesting to conduct more formal tests and validation of the voxel-wise SEM approach used in this study, as well as the ability of the AFNI multiple comparisons approach to appropriately correct for these issues. Methodological advances for relating latent variables to brain constructs are greatly needed in the clinical neuroscience field currently, where there is now a lot of interest in examining the neural correlates of these broad transdiagnostic constructs.

4.6 Conclusion

These data provide novel preliminary correlational evidence suggesting that the general and internalizing psychopathology factors are associated with individual differences in activation to reward anticipation in the MID task. Consistent with our hypothesis, activation in the anticipation phase of the MID in the right dorsal ACC was associated with the general factor of psychopathology. Inconsistent with our hypothesis, no effects were found in other brain regions from the reward network, for either the anticipation or attainment stages, for any other higher-order dimension. Additionally, I identified several regions not in the reward network for which activation in the reward anticipation stage was associated with higher order psychopathology. Further work is needed to identify and characterize the nature of these regions, and whether these findings are replicable.

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