NEURAL REWARD FUNCTIONING IN BIPOLAR SPECTRUM DISORDERS AND SUBSTANCE USE DISORDERS: IDENTIFYING COMMON MECHANISMS

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ABSTRACT

Bipolar spectrum disorders (BSDs) and substance use disorders (SUDs) are highly co-occurring and both are associated with dysfunction in neural networks that mediate reward processing and motivated behavior. Furthermore, despite their high comorbidity rate, limited research into their shared neural mechanisms or potential prospective risk factors exists. This study attempted to elucidate common neural pathways for these disorders, and adds to the small but growing literature on possible prospective predictors of these disorders.

We employed a task-based functional magnetic resonance imaging (fMRI) study to examine regions-of-interest (ventral striatum [VS], orbitofrontal cortex [OFC], ventromedial prefrontal cortex [vmPFC], dorsolateral prefrontal cortex [dlPFC]) and connectivity (VS-OFC, VS-vmPFC, vmPFC-dlPFC) analyses to examine neural reward processing as potential predictors of future substance and mood symptoms, and to explore differences among groups of participants with and without BSDs and SUDs. Results from this study provided evidence that blunted activation in the VS and dlPFC and greater negative connectivity between the vmPFC and dlPFC, key reward and control circuits, is implicated in prospective substance use. However, we did not find evidence to support our hypothesis that reward-related neural responses predict BSD symptoms or could differentiate individuals with co-occurring BSDs and SUDs from healthy volunteers. The study highlights the importance of larger, longitudinal studies to more fully probe neurodevelopmental trajectories in mood, substance, and related disorders.

We also conducted an extensive review of the neural reward literature in BSDs and SUDs to understand possible pre-existent mechanisms. Results of the review

provided support for an equifinality/multifinality perspective in that similar neural reward processing dysfunctions can lead to both BSDs and SUDs and different neural reward processing abnormalities can lead to a single outcome (e.g., SUDs). Taken together, results from the dissertation address an important gap in the literature on BSD-SUD comorbidity, suggest possible shared mechanisms that predispose to both disorders, and provide a backdrop for future work in this area to inform more theoretically-targeted interventions and prevention.
Keywords: Bipolar spectrum disorders, substance use disorders, reward processing, comorbidity, functional magnetic resonance imaging

DEDICATION

For my mom, who not only inspired my career in clinical psychology, but who shaped me into the person I am today. She ingrained in me a set of values that have allowed me to become a better scientist and clinician, and her unconditional love and support provided me the strength and determination to complete my studies, stay true to my authentic self, and pursue my dreams.

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CHAPTER 1

MANUSCRIPT IN JOURNAL ARTICLE FORMAT

Introduction

Bipolar spectrum disorders (BSDs) and substance use disorders (SUDs) are highly co-occurring; SUDs are present in over a third of people with BSDs (Merikangas et al., 2011). This high comorbidity exacerbates the impacts on health and functioning compared to either disorder alone. For example, individuals with co-occurring BSDs and SUDs have worse outcomes including more hospitalizations, poorer treatment course, increased suicidality, and work disability (Goldberg, Garno, Leon, Kocsis, & Portera, 1999; Hoblyn, Balt, Woodard, & Brooks, 2009; Oquendo et al., 2010; Post et al., 2003; Wilk, West, Rae, & Regier, 2006). Although this comorbidity is incontrovertible, the cause is much less clear (Post & Kalivas, 2013). Understanding the underlying neural mechanisms of both disorders is critical to inform our understanding of common neurobiological pathways and to develop new therapeutic targets. Identification of neural mechanisms that represent either pre-existing risk factors or corollaries of these disorders would inform our understanding of the onset and course of BSDs and SUDs, and may help clarify why they so frequently co-occur.

Reward sensitivity, the level of one's approach motivation towards goals and rewards, is associated with the onset and course of both BSDs (Alloy, Bender, et al., 2012; Alloy, Urošević, et al., 2012; Nusslock, Alloy, et al., 2012) and SUDs (Alloy et al., 2009; Dawe, Gullo, & Loxton, 2004; Dawe & Loxton, 2004), and represents an important avenue for exploration. For example, disruption in the neural circuitry that mediates

reward, motivation, and goal-directed behaviors may increase vulnerability to both BSDs and SUDs, and thus, may represent a similar pathophysiology for both disorders. Although BSDs are known to be associated with reward hypersensitivity (Alloy, Nusslock, & Boland, 2015; Johnson, Edge, Holmes, & Carver, 2012; Nusslock & Alloy, 2017), there is conflicting evidence about whether SUDs arise from reward hypo- or hypersensitivity (Nusslock & Alloy, 2017). Nonetheless, there is evidence that self-reported reward sensitivity is associated with BSDs and SU over time, and partially explains the prospective comorbid relationship between BSDs and SUDs (Alloy et al., 2009). Thus, investigating neural mechanisms of reward function involved in both BSDs and SUDs may shed light on common etiological pathways.

Neural Circuits Involved in Reward Processing

The fronto-striatal circuit is a key component of the brain's reward system, consisting of regions implicated in motivated behavior towards obtaining rewards, and subsequently, in processing hedonic value of these rewards once obtained (Mason, O'Sullivan, Montaldi, Bentall, & El-Deredy, 2014). This circuit is facilitated by dopamine transmission, which aids in reinforcement and learning. The circuit consists of the ventral striatum (VS; including the nucleus accumbens or NAcc, the ventral medial caudate, and the rostroventral putamen), as well as higher-level structures like the orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC; Haber & Knutson, 2010). The VS plays an important role during the anticipation phase of both primary and secondary (e.g., monetary) reward processing, whereas the OFC may be important in determining the likelihood of a reward outcome, and encoding incentive value at the time of decision-making (Diekhof, Nerenberg, et al., 2012; Knutson, Taylor,

Kaufman, Peterson, & Glover, 2005). The vmPFC reflects subjective preference and behavioral choice during reward-related decision-making, and serves as a major relay center between the striatum and more frontal brain regions related to cognitive control (Mason et al., 2014). For example, the dorsolateral PFC (dlPFC), situated within the cognitive control circuit, integrates motivation information from the striatum with cognitive control demands (Leon & Shadlen, 1999).

Although the cognitive control and reward networks have been conceptualized as two separate systems in adolescent brain development, the maturation of these circuits is related to the development of behavioral control, inhibition, and goal-oriented decisions (Steinberg, 2010). Thus, investigating connectivity between these two key networks may have important implications for understanding the neural mechanisms involved in SUDs and BSDs, which are both associated with impulsivity and risky behaviors. Connectivity between fronto-striatal regions is critical for the development of behavioral control and this is specifically mediated by increased vmPFC and dlPFC connectivity (Steinbeis, Haushofer, Fehr, & Singer, 2016), as the vmPFC is the region in which signals converge from the VS and dlPFC, thus serving as an important "relay" center between the two circuits (Leon & Shadlen, 1999). The vmPFC and dlPFC are connected and exchange information during reward-relevant contexts, such as during temporal discounting (Hare, Hakimi, & Rangel, 2014; Sokol-Hessner, Hutcherson, Hare, & Rangel, 2012). For example, it is thought that in reward contexts, the vmPFC serves to encode the reward, and passes this information to the dlPFC, which then determines the behavioral response (Campbell-Meiklejohn, Woolrich, Passingham, & Rogers, 2008; Hare, Camerer, & Rangel, 2009). Given the strong associations between these regions, aberrant responding

and connectivity within and between the reward and control circuits may influence the development of disorders associated with maladaptive motivated behaviors, such as BSDs and SUDs.

Different components of reward stimuli also contribute to responsivity within the neural reward circuit, particularly during anticipatory phases in the nucleus accumbens (Knutson & Cooper, 2005). For example, the two-factor theory states that two separate factors, valence and salience, both play a role in activating neural reward regions during reward processing (for review see Cooper & Knutson, 2008; Tye, 2018). Valence reflects the hedonic value of a stimulus, or in other words, whether a reward is "good" or "bad." Proponents of this account argue that neural activation, particularly within the nucleus accumbens, increases with the positive magnitude of anticipated rewards, and thus, positive arousal and emotional states will guide approach behavior towards rewards (Knutson, Rick, Wimmer, Prelec, & Loewenstein, 2007). This view also states that the reverse is true; the more negatively valenced a reward cue is, the lower the activation in the nucelus accumbens, which guides avoidance behavior away from punishment or losses (Tom, Fox, Trepel, & Poldrack, 2007). On the other hand, reward-related neural activation may not only depend on how positive or negative a stimulus is, but instead reflects the relative "importance" of a stimulus (salience) and is associated with arousal. Importantly, evidence demonstrates that both valence and salience drive reward-related brain activity, particularly during reward anticipation (Bartra, McGuire, & Kable, 2013; Kahnt, Park, Haynes, & Tobler, 2014; Zink, Pagnoni, Chappelow, Martin-Skurski, & Berns, 2006).

Neural Reward Dysfunction as a Potential Risk Factor for BSDs and SUDs

Reward processing abnormalities have been well documented in both BSDs and SUDs across a wide array of methods and measures, including self-report, behavioral, neurophysiological, structural and functional imaging (Harmon-Jones et al., 2008, 2002; Mason et al., 2014; Nusslock & Alloy, 2017; Strakowski, Adler, & DelBello, 2002; also see Chapter 2 for associated literature review). BSDs generally have been associated with reward hypersensitivity, as illustrated by increased reward-related activation in the striatum and in ventromedial prefrontal regions relative to healthy controls (Alloy, Boland, Ng, Whitehouse, & Abramson, 2015; Alloy, Olino, Freed, & Nusslock, 2016; Chase et al., 2013; Johnson et al., 2012; Phillips & Swartz, 2014). Furthermore, a recent imaging study using resting-state data found that people with BSDs had significantly stronger connectivity between the VS and vmPFC than healthy controls (Whittaker, Foley, Ackling, Murphy, & Caseras, 2018). There also is evidence for aberrant brain function in more frontal regions (i.e., dlPFC) associated with risk for BSDs. Indeed, decreased activity and volume in the dlPFC is associated with BSDs (Gruber, Rogowska, & Yurgelun-Todd, 2004; Lyoo et al., 2006) and activation of the dlPFC may be an important protective factor against the development of BSDs and other mental health issues. For example, individuals at high genetic risk for BSDs exhibit lower recruitment of the dlPFC during sustained attention tasks, and larger dlPFC volumes differentiated healthy probands from their BSD-affected siblings (Eker et al., 2014). Finally, activating the dlPFC during a laboratory risk-taking task (Balloon Analogue Risk Task) diminished risky choices in favor of safer ones (Fecteau, Knoch, et al., 2007; Fecteau, Pascual-Leone, et al., 2007).

Thus, BSDs may be characterized by an abnormal interplay between cortical and striatal regions, where the weighting of neural signals (occurring in the vmPFC) is biased towards the VS and away from the dlPFC, which is responsible for exerting top-down control over limbic regions (Mason et al., 2014). In one study, researchers found a decoupling between the dlPFC and medial PFC regions in BSDs compared to controls during resting-state scans (Chai et al., 2011). Additionally, in studies on euthymic individuals with BSDs, monetary reward processing is associated with increased activation in and connectivity between the VS and OFC, as well as decreased connectivity between the VS and more anterior PFC regions (Dutra, Man, Kober, Cunningham, & Gruber, 2017; Nusslock, Alloy, et al., 2012; Schreiter et al., 2016). Thus, this suggests that BSDs may be associated with hyperactivation and strong connectivity in the striatal and medial PFC regions (i.e., OFC, vmPFC) of the reward circuit, but decreased activation and connectivity between these regions and PFC regions associated with executive control.

Reward processing also is disrupted in individuals with SUDs. A recent meta-analysis demonstrated that people with SUDs show an overall blunted neural response during monetary reward processing (Luijten, Schellekens, Kühn, MacHielse, & Sescousse, 2017). Additionally, people who have relapsed on cocaine show significantly lower activation in the bilateral striatum on a reward learning task compared to their abstinent counterparts (Stewart et al., 2014). However, substances of abuse cause neuroadaptations in the brain, which result in lasting changes in reward circuitry, thus, making this circuit less stimulated by non-drug related reward cues (Volkow, Koob, & McLellan, 2016). Therefore, blunted reward responses may be a consequence of

prolonged substance use in people with SUDs. In line with this notion, one study that examined initiation of substance use in an adolescent sample who never used substances found evidence that hyperactivation in the striatum conferred risk for substance use initiation (Cope, Martz, Hardee, Zucker, & Heitzeg, 2019). Although a review of monetary reward processing findings in SUDs found that most studies demonstrated blunted VS activity associated with SUDs, there is significant discrepancy among findings (Balodis & Potenza, 2015). Specifically, the authors argue that the divergence of reward processing findings (specifically associated with the VS) could be indicative of individual differences in connectivity between frontal and striatal regions (Balodis & Potenza, 2015). Indeed, there is evidence that abnormal responding in fronto-cortical regions is associated with substance use. For example, decreased vmPFC activation on a response inhibition task has been shown to be predictive of substance use in adolescents (Mahmood et al., 2013). However, much like the ROI literature, findings for connectivity between the reward circuit and frontal control regions also are mixed, with some suggesting decreased connectivity between the VS and medial portions of the PFC as well as the dlPFC in people with SUDs (Crane et al., 2017; Motzkin, Baskin-Sommers, Newman, Kiehl, & Koenigs, 2014), and others finding increased connectivity between the NAcc and cognitive control network is associated with earlier substance use onset in adolescence (Weissman et al., 2015). Although seemingly contradictory, these studies support the hypothesis that initial onset of substance use in adolescence may be driven by hypersensitivity of the reward network (Cope et al., 2019; Weissman et al., 2015), but that over time, and with drug-induced desensitization, people who develop clinically

significant SUDs start to exhibit hypoactivation during reward processing (Crane et al., 2017; Luijten et al., 2017; Motzkin et al., 2014; Volkow et al., 2016).

The Current Study

Understanding reward-related brain function in BSDs and SUDs has the potential to inform our understanding of the mechanisms involved in the onset of, or worsening of course, for both BSDs and SUDs. Very few studies have examined neural reward activity as a predictor of future BSD and SUD symptoms and disorders. There have been no prospective studies predicting onset of first BSD episode, likely because accurate diagnosis of BSD can take years, and many are initially misdiagnosed with unipolar depression (Goodwin & Jamison, 2007; Pendergast et al., 2014). However, elevated left frontal EEG activity predicts conversion to more severe forms of BSD (i.e., Bipolar I; Nusslock, Alloy, et al., 2012), and elevated structural connectivity between the NAcc and medial OFC is found in individuals with self-reported hypomania proneness who are at elevated BSD risk (Damme, Young, & Nusslock, 2015). Additionally, a handful of studies examining onset of SUDs prospectively provides evidence for both hyper- and hypo-activity during reward processing. These studies suggest that differences in activation in both striatal and cortical regions, aberrant functioning in the mesolimbic reward motivation system, as well as impaired prefrontal control may confer risk to future SUD (Baker et al., 2019; Büchel et al., 2017; Whelan et al., 2014). Again, given methodological issues, some of these studies included individuals who had already initiated substance use, whereas others did not.

Although much research examines neural responding to reward in BSDs and SUDs separately, no study has directly compared reward processing between groups of

individuals with a BSD only and with a SUD only. The above evidence points to potentially similar neural mechanisms that underlie both BSDs and SUDs. Specifically, although individuals with SUDs may have hypoactivation, whereas individuals with BSDs may have hyperactivation in limbic reward regions, there is evidence for diminished connectivity between the fronto-striatal reward circuit and prefrontal regions associated with executive control in both disorders. Hence, it is possible that these disorders may have both similarities and dissimilarities in brain regions associated with modulating goal-directed and motivated behavior. The current study aims to examine these similarities and differences in neural reward function related to BSDs and SUDs in a variety of ways. First, we will examine reward functioning as a potential prospective predictor of future mood and substance problems. Additionally, this study is novel in that it is the first to directly compare neural responses during reward processing in people with BSDs and SUDs during a reward processing fMRI task. Thus, we aim to inform our understanding of the neural mechanisms that confer vulnerability to BSD and SUD symptomatology. The literature supports the predominant role of the anticipation phase of reward processing in both BSDs and SUDs, as well as in primary reward fronto-striatal regions' involvement in processes related to incentive salience (i.e., NAcc; Cooper & Knutson, 2008; Zink, Pagnoni, Martin-Skurski, Chappelow, & Berns, 2004). Additionally, reward anticipation is particularly relevant to the development of SUDs, because drug expectancy plays an important role in craving and attentional bias towards drug cues (Jędras, Jones, & Field, 2013). Thus, the hypotheses outlined below focus on reward anticipation specifically during reward vs. no reward contrasts.

Hypothesis 1. Given the extant literature on reward function in people with BSDs, as well as the small body of literature that examines BSD risk and conversion to more severe BSDs, I hypothesized (1a) that elevated activation in the VS, OFC, and vmPFC and blunted activation in the dlPFC would be associated with higher rates of prospective hypomania and depression symptoms. There also is evidence that suggests enhanced connectivity within the reward circuit as well as diminished connectivity between the reward circuit and prefrontal control regions is associated with BSDs and in those at potential risk for BSDs. Therefore, I hypothesized (1b) that elevated connectivity between the VS and OFC and between the VS and vmPFC would be associated with increased prospective hypomanic and depressive symptoms. In contrast, I hypothesized that low connectivity between the vmPFC and dlPFC would be associated with increased prospective hypomanic and depressive symptoms. I posited that similar neural reward processing patterns would predict both hypomania and depression symptoms given research indicating these patterns are a vulnerability for and a mood-independent trait of BSDs (Alloy et al., 2016; Dutra et al., 2017a; Nusslock, Alloy, et al., 2012; Schreiter et al., 2016).

Hypothesis 2. Given the extant literature supporting reward hyposensitivity in individuals with an existing SUD, and as a risk factor for prospective SUDs, I hypothesized (2a) that blunted activation across all four regions would be associated with future problematic substance use. Similarly, given the extant literature supporting decreased connectivity throughout reward and control circuits in individuals with SUDs, I hypothesized (2b) that low connectivity between the VS and OFC, the VS and vmPFC, and the vmPFC and dlPFC would be associated with future problematic substance use.

Exploratory Question 1. I explored group differences in neural activation and connectivity within the fronto-striatal reward circuit regions (i.e. VS, OFC, vmPFC) and dlPFC during reward processing among three groups: those with a history of SUDs, but who have not been diagnosed with a BSD at time of scan (N = 22), those with a history of BSD, but who have not been diagnosed with a SUD at time of scan (N = 15), and a healthy comparison (HC) group who have not been diagnosed with either a mood disorder or SUD (N = 22). In a subsequent analysis, I also included a fourth group of individuals with comorbid BSDs and SUDs (N = 11).

Given the small sample sizes for each group, these analyses were conducted on an exploratory basis. Consistent with the extant literature on reward hypersensitivity in BSDs, I hypothesized that the BSD group would exhibit significantly higher activation in the VS, OFC, and vmPFC during reward processing compared to HC and SUDs, and decreased activation in the dlPFC during reward processing relative to HC (but no difference from the SUD group). Conversely, consistent with the literature on blunted reward responsivity in individuals with pre-existing SUDs, I hypothesized that the SUD group would exhibit significantly lower activation in the VS, OFC, and vmPFC compared to BSDs and HCs, and significantly lower activation in the dlPFC during reward processing relative to HC (but no different from the BSD group).

In terms of fronto-striatal connectivity, I hypothesized that the BSD group would exhibit significantly greater connectivity during reward processing between the VS and OFC and between the VS and vmPFC than the SUD and HC groups. I also hypothesized that the BSD group would exhibit significantly less connectivity between the vmPFC and dlPFC during reward processing than the HC group (but no different from the SUD

group). On the other hand, based on the literature on reward processing in people with pre-existing SUDs, I hypothesized that the SUD group would exhibit significantly less connectivity during reward processing between the VS and OFC and between the VS and vmPFC than the BSD and HC groups. I also hypothesized that the SUD group would exhibit significantly less connectivity between the vmPFC and dlPFC during reward processing than the HC group (but no different from the BSD group). Finally, given the literature indicating that substances of abuse exert neuroadaptations on the brain's reward circuit, I hypothesized that the comorbid BSD and SUD group would exhibit similar activations and connectivity as the SUD only group.

Exploratory Question 2. I explored whether behavioral results from the monetary incentive delay (MID) task (reaction time and hit rate), differentiate between groups (BSD, SUD, HC) and whether they are significant predictors of future mood and substance symptoms. Given the preponderance of literature demonstrating reaction times on the MID are not significantly associated with differences among various psychiatric groups, I hypothesized that the MID behavioral results would not significantly distinguish between groups, or predict prospective mood/substance symptoms (Jia et al., 2011; Karoly et al., 2015; Knutson & Greer, 2008).

Methods

Participant Recruitment

Participants in the current study included 133 individuals recruited from the larger Teen Emotion and Motivation (TEAM) project. Participants ages 14-19 were recruited from Temple University undergraduates and Philadelphia-area high school students over 3.5 years, and were followed approximately every 6 months as part of the larger

prospective Project TEAM. Following procedures in Alloy et al. (2012), students were screened on demographics and two self-report BAS/reward sensitivity measures: the Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) Scales and the Sensitivity to Punishment/Sensitivity to Reward Questionnaire (SPSRQ). During this initial screening process (Phase I), students scoring in the highest 15th percentile on both the BAS-Total (high BAS-T score cutpoint $\geq$ 43) and Sensitivity to Reward (SR) scale (high SR cutpoint $\geq$ 16) were categorized as High BAS (HBAS). Participants were classified as Moderate BAS (MBAS) if they scored between the 40th and 60th percentiles on both the BAS-T (cutpoints $\geq$ 37 and $\leq$ 39) and SR (cutpoints $\geq$ 10.4 and $\leq$ 12.6) subscales. Of 9991 Phase I students, 7.77% (n = 776) qualified for HBAS and 4.04% (n = 404) for MBAS status. Those meeting eligibility requirements based on scores were invited to participate in a second screening visit (Phase II). During Phase II, participants underwent diagnostic assessments and were excluded if they had a lifetime history of any BSD or psychotic disorder. This is because the major aim of Project TEAM was to predict initial onset of BSDs; however, participants who met criteria for BSD at baseline were not excluded in the present study. After screening procedures, eligible participants were invited to participate in a baseline visit (Time 1), during which they completed multiple self-report and behavioral measures assessing reward sensitivity, impulsivity, cognitive style, emotion regulation, social rhythms, current mood symptoms, and lifetime and family history of psychopathology. Participants were followed prospectively every 6 months and completed assessments of reward-relevant life events, mood and substance use symptoms and diagnoses, cognitions, emotions, personality, and social rhythms.

Approximately six years after Project TEAM began, a subset of participants (aged 18 and over) who completed Time 1 assessments were invited to participate in an additional MRI component of the study. For the MRI study, we attempted to recruit evenly into three groups (MBAS, HBAS, and HBAS + BSD). Standard exclusion criteria were applied to participants completing the MRI component (presence of ferrous metal in the body, serious medical conditions, claustrophobia, left-handedness, and pregnancy). Participants also were asked to provide a report of history of head trauma and medication usage (both prescribed psychotropic medications, non-psychotropic medications, and over-the counter medications). Participants were screened using a standardized MRI screening protocol conducted by a certified MRI technician. Participants completed a set of trait-based self-report measures within two days prior to the MRI, as well as a set of state-based self-report measures on the day of the MRI scanning session. Participants completed a set of behavioral tasks in the scanner.

Current Study Participants

In total, 139 participants from Project TEAM consented and were scheduled to take part in the MRI portion of the study. However, of these 139 participants, six were excluded because they were unable to complete the MRI scan (i.e., one voluntarily withdrew, and five were unable to complete the study due to technical issues on the day of the scheduled scan). Of the 133 participants who completed the MRI scan, 26 were excluded due to excessive head motion (>3mm of movement across either run of the MID task), and four were excluded due to behavioral task acquisition errors (i.e., these participants completed one long MID run, instead of two separate runs described below). Thus, 103 participants had interpretable brain and behavioral data. However, 12

participants did not complete a post-MRI follow-up visit and could not be included in longitudinal analyses. Therefore, final $N = 91$ for longitudinal analyses testing Hypotheses 1 and 2. Of the 103 participants with usable imaging data, we identified participants based on history of BSD and SUD for inclusion in groups for our exploratory analyses. Individuals with a history of any SUD (i.e., alcohol, drug, combined alcohol/drug), but no history of a BSD, were categorized in the SUD only group (N = 22). Likewise, participants who had a pre-scan history of a BSD, but not SUD, were categorized in the BSD only group (N=15). Individuals who completed the MRI scan and did not have any diagnosed mood disorder or SUD history, and were not taking psychotropic medication at the time of scan were categorized as healthy controls (N = 22). Finally, individuals meeting criteria for both a SUD and BSD by the time of the scan were categorized into a combined BSD+SUD group (N = 11). Thus, our total sample size for group analyses was 70. Some participants included in group analyses were not included in longitudinal analyses and vice versa (i.e., a participant may have been categorized in a group, but not have follow-up data), thus total sample size across both sets of analyses was $N = 99$.

Measures

Reward Sensitivity

The Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) Scale (Carver & White, 1994) was used during screening to assess eligibility. The BIS/BAS Scale is a widely used self-report measure of trait levels of the behavioral activation and inhibition systems. The measure consists of 20 Likert items (1=strongly disagree, 4=strongly agree). The BAS scale measures reward-relevant constructs such as

goal-striving, fun-seeking, and reward-responsiveness. The total BAS score was used to determine eligibility for the Moderate and High BAS groups. It had acceptable internal consistency in the screening sample (α = .80), and has been shown to have acceptable retest reliability (Meyer, Johnson, & Winters, 2001).

The Sensitivity to Punishment Sensitivity to Reward Questionnaire (SPSRQ; Torrubia, Ávila, Moltó, & Caseras, 2001) also captures reward inhibition/activation sensitivities and was collected during screening. It is a self-report measure consisting of 48 "yes" or "no" questions. Scores from the 24-item reward (SR) subscale were used to determine eligibility for the Moderate and High BAS groups, along with BAS total scores. Torrubia et al. (2001) report acceptable internal consistency (αs = .75-.83) and good retest reliability for both subscales. The SR subscale had acceptable internal consistency (α = .76) in our sample.

Psychopathology Assessment

The Expanded Schedule for Affective Disorders and Schizophrenia-Lifetime and Change (SADS-L/SADS-C; Alloy et al., 2008; Endicott & Spitzer, 1978) interviews were used to diagnose lifetime and current Axis I disorders based on *DSM-IV-TR* and research diagnostic criteria (RDC). Intraclass correlations of interrater reliability are generally high (ICC = .6 or greater for 82% of diagnostic subscales; Endicott & Spitzer, 1978). Expanded versions of the interviews were used in this study to allow for *DSM-IV-TR* as well as RDC diagnoses and to probe additional information regarding mood episode duration and severity. These interviews were administered by trained diagnosticians, who were blind to BAS risk group. The expanded SADS-L was administered at baseline to assess lifetime psychopathology and the expanded SADS-C was administered at each six-

month follow-up to assess new diagnoses since the last interview. Participants who met either *DSM-IV-TR* or RDC criteria for Bipolar I, Bipolar II, Bipolar NOS, or cyclothymia were classified as having a BSD. Participants who met *DSM-IV-TR* or RDC criteria for alcohol and/or drug abuse or dependence were classified as having SUD. Interrater reliability for the SADS-L was good for both depression and bipolar diagnoses ($\kappa > .90$ and >.96, respectively; (Alloy et al., 2008; Alloy et al., 2000). Similarly, interrater reliability for the SADS-C was $\kappa > .80$ (Alloy et al., 2008).

Substance Use Symptoms

The Adolescent Alcohol and Drug Involvement Scale (AADIS; Moberg, 2003) is a two-part (drug and alcohol) self-report measure with 27 items that assess frequency of drug and alcohol involvement, and was specifically designed for use in research. It was validated in a sample of juveniles at University of Wisconsin (Moberg, 2003). The AADIS was completed at baseline, at each follow-up, and at the time of the MRI scan.

The Short Inventory of Problems-Revised (SIP-R; Blanchard, Morgenstern, Morgan, Labouvie, & Bux, 2003) is a self-report measure consisting of 30 items that assess problems associated with alcohol and drug use over the past month ("I have failed to do what is expected of me because of my drinking or drug use," "My family has been hurt because of my drinking or drug use."). The scale consists of 4-point Likert items (0 = never, 1 = 1-2 times/month, 3 = twice a week, 4 = daily/almost daily). Reliability at our first follow-up was excellent ($\alpha = .91$). The SIP-R was administered at each follow-up.

Depressive Symptoms

The Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996) is a 21-item self-report measure assessing depression symptoms in a variety of domains (affective,

cognitive, motivational, somatic). It is widely used to assess depressive symptom severity and treatment outcome in clinical samples, and consistently has shown good internal and retest reliability in nonclinical samples (Beck, Steer, & Garbin, 1988). In our Phase II sample, $\alpha = .89$. The BDI was administered at baseline, at each follow-up, and at the time of the MRI scan.

(Hypo)manic Symptoms

The Altman Self Rating Mania Scale (ASRM; Altman, Hedeker, Peterson, & Davis, 1997) is a self-report measure consisting of five Likert scale items (ranging from 0 – 4) that capture symptoms of (hypo)mania including elevated mood, increased self-confidence, decreased need for sleep, heightened psychomotor activity, and talkativeness. A single total score is calculated by summing the items. The measure is highly correlated with other clinical and self-report measures of (hypo)mania (Altman, Hedeker, Peterson, & Davis, 2001), and had acceptable internal consistency in our Phase II sample ($\alpha = .75$). The ASRM was administered at baseline, at each follow-up, and at the time of the MRI scan.

Handedness

The Chapman and Chapman Handedness Questionnaire (Chapman & Chapman, 1987) was used to assess handedness. Because there exists potential neurological lateralization differences between right and left handed individuals, individuals reporting left-handedness were excluded from the MRI scan. The questionnaire consists of thirteen items asking the participant to identify which hand they use to complete a variety of tasks (e.g., writing, using a hammer or toothbrush), with 1 = right hand, 2 = either hand, and 3 = left hand. Items are summed, and a final score is generated for each participant, with

the lowest possible score (13) being strongly right handed, and highest possible score (39) being strongly left handed.

Medication Use

On the day of the scan, participants were asked to complete a questionnaire asking if they take any prescription or over-the-counter medications, vitamins, or herbal supplements. Participants recorded the name, dose, frequency, route of administration, when they began taking each medication, and when their last dose was. For the current study, we noted medication use as a dichotomous variable (0 = not taking psychotropic medication within the past two weeks of scan, 1 = taking psychotropic medication within the past two weeks of scan).

fMRI Monetary Incentive Delay (MID) Task

Participants completed the MID task [(Samenez-Larkin et al., 2007); Figure 1]. First, a circle cue signaling a reward trial (the participant has the opportunity to Win $0.00, Win $1.50, or Win $5.00) or a square cue indicating a loss trial (the participant might Lose $0.00, Lose $1.50, or Lose $5.00) was presented for 2s. Then, a jittered fixation was presented followed by a solid white square. Participants were instructed to make a button response when the solid white square was still on the screen to either win money (reward trials) or avoid losing money (loss trials). Participants were presented with feedback detailing the amount of money won or lost on each trial for 2s. Finally, a jittered fixation cross was presented for 2s, 4s, or 6s as an intertrial interval. The initial target duration was calculated from each participant's mean hit reaction time on a MID practice run completed before entering the scanner. The target duration dynamically updated during the MID task to maintain task difficulty so that participants accurately hit

the target on 66% of trials, calculated separately for each trial type (i.e., Win $0.00, Win $1.50, Win $5.00, Lose $0.00, Lose $1.50, Lose $5.00). The six trial types each were presented 8 times in random order, totaling 96 trials, across two MID runs.

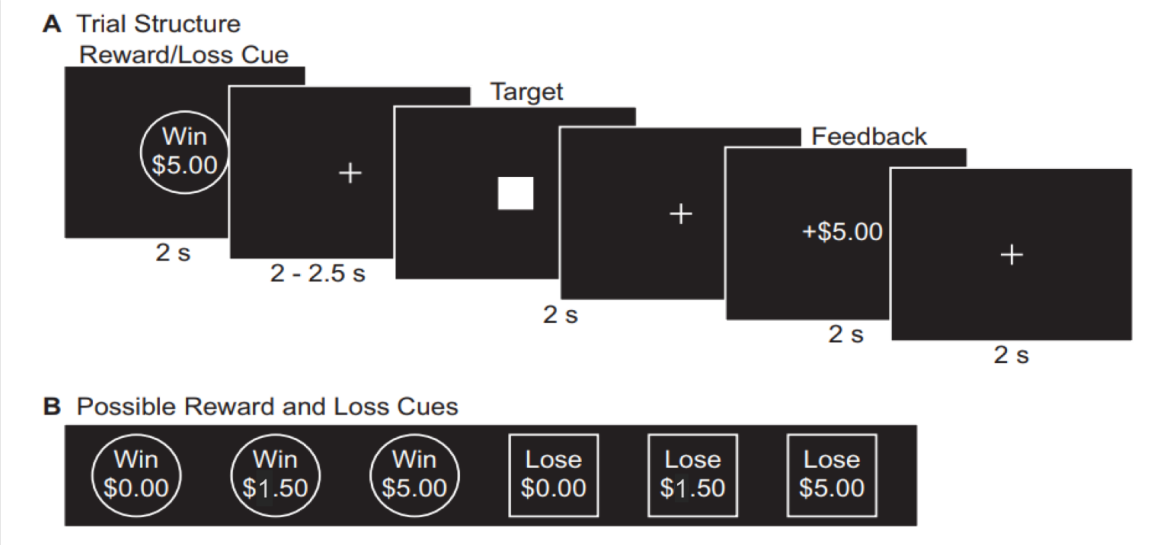

Figure 1. The (A) trial structure and (B) possible reward and loss cues of the monetary incentive delay (MID) task used to examine reward and loss anticipation and outcome (adapted from: Young & Nusslock, 2016).

fMRI Data Acquisition

Before entering the scanner, participants completed questionnaires, an MRI safety screener, and practice runs for the MID task. Neuroimaging data were collected using a 3.0 Tesla Siemens Verio wide-bore MRI scanner with a standard 12-channel head coil at Temple University Medical Center. Imaging sessions were conducted jointly by TUMRIC MRI technicians who were responsible for operating the MRI, and trained Project TEAM graduate-level research assistants. Stimulus presentation during the MID was conducted using E-Prime software (Schneider, Eschman, & Zuccolotto, 2002). A rear-projection system was used, and behavioral responses were collected using a fiber optic response pad. The MRI scan began with a 10s localizer to ensure proper head

position. Next, participants completed a 10-minute, eyes open resting state scan, followed by the MID task (two runs consisting of 48 trials each). Functional BOLD scans were collected using the following parameters: coverage = 36 axial slices, 4mm thick (FOV = 236 mm), matrix = 64x64, voxel size = 3.7 x 3.7 x 4.0 mm, TR = 2000, TE = 25 ms, Flip Angle = 70°, acquisition volumes = 292. We then collected structural 3D MPRAGE scans in the sagittal plane using the following parameters: voxel size = 0.5 x 0.5 x 1.0 mm, TR = 1600ms, TE = 2.46ms, FOV = 252, Flip Angle = 9°, 176 volumes. Finally, a DTI 64-direction scan was collected. Total scan time was approximately one hour.

Neuroimaging Analyses

Image Preprocessing

All pre-processing was carried out in SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK) using standard procedures. First, functional images were realigned and corrected for errors in slice-timing. Images then were spatially normalized to MNI space and smoothed using a 6 mm full width at half maximum (FWHM) Gaussian kernel. Motion parameters were extracted along 3 rotational dimensions (pitch, roll, yaw), and 3 translational dimensions (x, y, z). Participants who had >3mm head movement along any dimension on either run of the MID task were excluded from further analyses. High pass temporal filtering was applied at 128 s.

Regions-of-Interest analyses

A first-level model was constructed for each participant in which the hemodynamic signal was deconvolved using a general linear model. Twelve regressors were used to identify the six trial types (i.e., Win $0.00, Win $1.50, Win $5.00, Lose $0.00, Lose $1.50, Lose $5.00) during the MID anticipation and consumption phases.

The MID anticipation phase was defined as the period after presentation of the cue indicating the possibility to win or lose money but prior to presentation of the target square (2–2.5s). The MID consumption phase was defined as the period after receipt of feedback of winning or losing money (2s). Then, we included six variables of no interest for motion. At the second-level analysis, we combined data across the two MID runs for each participant using a fixed effect model. Finally, first-level voxel-wise *t*-statistics were generated for each participant contrasting reward (i.e., Win $1.50, Win $5.00) vs. non-reward (i.e., Win $0.00) trials to calculate reward anticipation and reward consumption conditions contrasted with non-reward baseline condition.

Parameter estimates (beta weights) were extracted from predefined regions-of-interest (ROIs) for reward anticipation. A functionally derived ROI for the bilateral VS was defined as two 8mm spheres based on MNI coordinates (right: x=9, y=9, z=–8; left: x=–9, y=9, z=–8) from a previous meta-analysis (Di Martino et al., 2008). We used an anatomically defined ROI for the bilateral OFC, ventromedial PFC, and dorsolateral PFC (using the Harvard Oxford Atlas). The averaged parameter value from across the entire ROI then was exported into SPSS and MPlus for further analyses. Specifically, ROI parameter estimates were used as independent variables in regression analyses to predict to prospective mood (BDI and ASRM) and substance (SIP and AADIS) symptoms. We also conducted ANCOVAs to examine group differences (SUDs vs BSDs vs HC; and SUDs vs BSDs vs HC vs SUDs + BSDs) in ROI activation (Exploratory Question 1).

Connectivity Analyses

All pre-processed functional data were imported into FSL to explore connectivity between the VS and prefrontal regions (i.e., OFC, vmPFC) and between frontal regions

of the reward circuit and control network (i.e., vmPFC and dlPFC) using psychophysiological interaction (PPI) analyses (Friston et al., 1997; McLaren, Ries, Xu, & Johnson, 2012). PPI analyses allow us to examine context-specific changes in connectivity between specific brain regions. Thus, we could determine whether there were differences in communication between key regions related to reward processing, specifically during the anticipation context. Significant interactions allow us to determine whether reward anticipation contexts change how one brain region ("seed" region) affects another brain region ("target" region). First-level PPI models involved mainly the same anticipation regressors described above (i.e. Win and Lose $5, $1.50, $0); however instead of modeling consumption, we modeled both hit and miss, as well as valence and salience signals. Valence signals reflect the value of a stimulus and follow a linear pattern, whereas salience signals follow a quadratic trend reflecting higher activation for higher importance/absolute value of a stimulus (Bartra et al., 2013; Kahnt et al., 2014; Zink et al., 2006). Thus, if significant activation was found during reward anticipation, we further probed connectivity during valence and salience signals. We included an additional physiological regressor that represents the time course of activation within ROIs. We also included interaction terms between the physiological regressor and task regressors. The second-level analysis combined data from the two runs of the MID task for each participant using a fixed effects model. Of note, three participants were excluded from connectivity analyses that were not excluded from ROI analyses due to recording difficulties during acquisition of behavioral data; for these three participants hit-miss contrasts could not be modeled. The average time series of reward-related connectivity was extracted from the same predefined regions from ROI analyses using FSL's

fslmeants (VS "seed" – OFC "target;" VS "seed" – vmPFC "target," and vmPFC "seed" – dlPFC "target"). Parameter estimates then were exported into MPlus and SPSS for further analyses as described above.

Behavioral Analyses

Mean reaction times (RT) and hit rates (HR) were calculated based on valence (reward vs. loss), and magnitude ($0 or neutral, $1.50 or small reward/loss, and $5.00 or high reward/loss). The MID task sets accuracy at 66%; however, to include the maximum number of participants, we set our threshold at 50%, as mean total HR across trials was 54%. Any participant whose HR was outside this range was excluded from analyses. Individual RTs that fell below 200 ms or greater than 3 SDs from the mean for any one participant also were excluded based on guidelines for omitting RTs from spurious trials (i.e., responding before trigger, inattention; Whelan, 2008). A repeated measures two-way ANOVA was conducted with condition (valence/magnitude trial type) as a within-subjects factor, and diagnostic group (BSD, SUD, and HC) as the between-subjects factor. We also calculated the mean RT and HR for each valence/magnitude trial type per participant, and included them as independent variables in regression analyses predicting to prospective mood and substance symptoms.

Results

Clinical Characteristics of the Sample

First, we ran independent t-tests and chi-square tests to examine whether the total participants included in analyses (N = 99) differed from those who were excluded. Results from t-tests revealed that participants who were included did not differ from those excluded on BAS total or SR scores, $t(137) = 1.33$, $p = .19$, $t(137) = .60$, $p = .55$,

respectively, nor did they differ on any mood or substance use symptom measures at the time of the scan; AADIS $t(136) = -.59$, $p = .56$, BDI $t(134) = .96$, $p = .34$, ASRM $t(135) = -.13$, $p = .89$. Individuals included did not differ from excluded participants on age at scan, $t(134) = 1.16$, $p = .25$, handedness, $t(45.35) = -.44$, $p = .66$, gender, $\chi^2(1) = .01$, $p = .91$, race, $\chi^2(6) = 5.31$, $p = .50$, or whether participants were taking psychotropic medication at the time of scan, $\chi^2(1) = 1.00$, $p = .76$.

Given the relatively small sample size in our exploratory group analyses (N = 70), and uneven group sizes (SUD = 22, BSD = 15, BSD+SUD = 11, HC = 22), the assumptions for homogeneity of variances were violated for all one-way ANOVAs on continuous variables (except age and SR). Therefore, to examine group differences, we conducted Welch tests followed by Games-Howell post-hoc tests for significant results on all other continuous variables (BAS, handedness, AADIS, BDI, and ASRM). Similarly, because of small and unequal group sizes, we ran Fisher's exact t-tests instead of chi-square tests to compare groups on categorical variables. Because of the low incidence of individual non-white racial groups, for the purposes of group comparison, race was dichotomized (white vs. non-white). Descriptive and clinical characteristics for participants included in longitudinal analyses (N = 91) and in group analyses (N = 70) are in Table 1.

There was a significant main effect of group on substance use frequency (AADIS) at time of scan, Welch's $F(3, 30.53) = 7.82$, $p < .01$. As expected, Games-Howell post-hoc tests revealed that the SUD group had significantly higher AADIS scores at time of scan compared to the BSD group (mean differences = 4.54 ± 1.36, $p = .01$). The SUD+BSD group also had significantly higher AADIS scores compared to the BSD and

HC groups (mean difference = 7.95 ± 1.97, $p < .01$, 7.23 ± 2.02, $p = .01$, respectively). Interestingly, the SUD group only differed marginally from the HC group on AADIS scores at scan (3.82 ± 1.43, $p = .05$). Groups also differed on BAS scores, Welch's $F(3, 32.47) = 5.65$, $p < .01$, but only differed marginally on SR scores, Welch's $F(3, 66) = 2.22$, $p = .10$. Games-Howell post-hoc tests revealed that the BSD + SUD group had significantly higher BAS scores than the SUD group (mean difference = 4.91 ± 1.51, $p = .02$) and than the HC group (mean difference = 5.47 ± 1.42, $p < .01$). The groups differed on depression scores (BDI; Welch's $F(3, 26.70) = 5.01$, $p < .01$), and Games-Howell post-hoc tests revealed that both the SUD and BSD groups had significantly higher BDI scores than the HC group (mean difference = 4.73, $p = .03$, mean difference = 6.13, $p = .04$, respectively). There were no main effects of group for hypo/mania scores (ASRM), Welch's $F(3, 28.36) = 2.36$, $p = .09$, age, $F(3, 66) = 2.15$, $p = .73$, or handedness, Welch's $F(3. 27.82) = 1.40$, $p = .27$. Finally, Fisher's exact t-tests revealed no significant group differences on gender, Fisher's exact $t = .26$, $p = 1.00$, race, Fisher's exact $t = 13.38$, $p = .51$, or psychotropic medication use within 2 weeks of scan, Fisher's exact $t = 2.80$, $p = .53$.

Table 1. *Demographic and Clinical Sample Characteristics*

	Longitudinal (*n* = 91)	SUD (*n* = 20)	BSD (*n* = 15)	BSD+SUD (*n* = 11)	HC (*n* = 24)
Age, months (SD)	21.43 (2.16)	21.95 (2.52)	21.20 (1.93)	21.27 (2.37)	21.45 (2.09)
Female	51.6%	50.0%	53.3%	45.5%	50.0%
Race					
White	57.1%	72.7%	60.0%	63.6%	59.1%
Black	23.1%	18.2%	20.0%	0.0%	18.2%
Asian	9.9%	4.6%	13.3%	18.2%	13.6%
Bi/Multiracial	6.6%	0.0%	0.0%	9.1%	9.1%
Native American	1.1%	0.0%	0.0%	9.1%	0.0%
Other	2.2%	4.6%	6.7%	0.0%	0.0%
Handedness[a] (SD)	13.97 (1.44)	13.64 (0.79)	14.87 (2.23)	13.64 (1.29)	13.86 (1.70)
Medication Use	5.5%	4.5%	0.0%	9.1%	0.0%
ASRM (SD)	3.42 (3.50)	3.68 (3.11)	3.77 (3.47)	6.55 (5.89)	2.27 (2.53)
BDI (SD)[b]	5.31 (6.88)	7.28 (6.87)	8.68 (7.46)	5.73 (8.53)	2.55 (3.25)
AADIS (SD)[c]	6.15 (4.93)	8.41 (5.40)	3.87 (2.80)	11.82 (6.08)	4.59 (4.01)
BAS Total (SD)[d]	43.33 (4.64)	42.45 (4.75)	44.67 (3.27)	47.36 (3.70)	41.89 (4.16)
SR (SD)	15.52 (4.64)	15.12 (4.11)	16.47 (3.23)	18.36 (3.07)	15.20 (3.88)

Note. Medication Use = taking psychotropic medications within 2 weeks of scan; ASRM = Altman Self-Rating Mania Scale; BDI = Beck Depression Inventory; AADIS = Adolescent Alcohol and Drug Involvement Scale; BAS Total = Behavioral Activation Scale Total score; SR = Sensitivity to Reward score. [a]Chapman Handedness scores between 13 and 17 indicate right-handedness. [b]Significant group differences in BDI scores at scan (SUD > HC, BSD > HC); [c]Significant group differences in AADIS scores at scan (BSD+SUD > BSD, HC; SUD > BSD); [d]Significant group differences in BAS total scores (BSD + SUD > SUD, HC

Relationships Among Study Variables

Pearson correlations were conducted to examine the associations between continuous demographic/clinical variables (age, mood/substance symptoms, reward sensitivity, handedness) and activation in the VS, OFC, vmPFC, and dlPFC during reward anticipation as well as VS-OFC, VS-vmPFC, vmPFC-dlPFC connectivity during reward anticipation, and dependent variables in longitudinal analyses (mood and substance symptoms at follow-up; Table 2). Associations between independent variables and ROIs are reported for the entire sample (individuals included in both group and

longitudinal analyses, N = 99). Associations between independent variables and follow-up outcome measures are reported for our longitudinal sample (N = 91).

Regarding activation during reward anticipation in key ROIs, the only significant association was that dlPFC activation was associated positively with BAS total score $r(97) = .20$, $p < .05$. There were no significant associations between ROIs and SR, BDI, ASRM, AADIS, handedness, or age. Connectivity between the vmPFC and dlPFC during reward anticipation was associated negatively with race $r(94) = -.21$, $p = .04$. There were no other significant associations between VS-OFC, VS-vmPFC, or vmPFC-dlPFC connectivity and covariates. ASRM scores at follow-up were associated positively with BAS total score, ASRM at scan, AADIS at scan (rs(89) = .25 - .54), all ps < .05), and associated negatively with age at scan ($r(89) = -.28$, $p < .05$). BDI scores at follow-up were associated negatively with BAS total scores ($r(89) = -.24$, $p < .05$), and associated positively with BDI at scan ($r(89) = .73$, $p <.01$) and medication use at time of scan, $r(97) = .28$, $p < .05$). AADIS at follow-up was associated positively with ASRM and AADIS scores at scan (rs(89) = .27- .68), all ps < .01), as well as race (rs(89) = .39, $p < .01$), and associated negatively with age at scan ($r(89) = -.25$), $p < .05$) and gender (r(89) = -.25, p < .05). SIP scores at follow up were associated positively with BDI, ASRM and AADIS scores at scan (rs(89) = .25 - .59, all ps < .05), and associated negatively with race and gender (rs(89) = -.22, ps < .05).

Table 2. *Bivariate Correlations Between Demographic and Clinical Characteristics and Regions of Interests and Outcome Variables*

Measure	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1. BAS	.739**	-.057	-.071	-.067	.137	.124	-.033	-.091	.150	.021	.071	.084	.200*	-.018	-.047	-.116	.001	.115	-.238*	.246*
2. SR		-.135	016	-.049	.034	-.071	.099	-.093	.159	-.091	.027	.034	.139	-.031	006	-.093	.068	080	-.199†	.196†
3. Handedness			-.044	.063	.154	-.004	-.106	-.014	-.057	.109	.096	.193†	.106	-.205*	-.219*	-.080	-.004	145	.015	.071
4. Medication				.010	-.042	-.018	.167†	.067	.001	.021	.107	-.090	.081	.078	-.057	.009	.120	.032	.275*	-.147
5. Age					.167†	-.018	-.122	-.018	-.267**	-.102	-.029	.073	.112	.127	.142	-.031	-.247*	-.189†	-.041	-.283*
6. Race						.372**	-.346**	-.015	-.095	-.049	.050	.100	.105	-.201†	-.164	-.199†	-.439**	-.252*	-.018	-.166
7. Gender							-.289**	.130	-.062	.101	.018	.084	.069	-.182†	-.082	-.089	-.257*	-.144	.040	-.085
8. AADIS MRI								.157	.334**	-.119	-.030	.056	-.008	.062	.159	.094	.684**	.592**	.074	.375**
9. BDI MRI									.111	-.043	.186†	.084	.035	-.049	-.061	-.197†	.191†	.253*	.725**	.168
10. ASRM MRI										.074	.022	.053	.007	-.129	-.003	.005	.273**	.289**	.103	.541**
11. VS											.697**	.419**	.463**	-.184†	-.104	-.031	-.202†	-.177†	.049	-.005
12. OFC												.522**	.724**	-.231*	-.191†	-.156	-.047	-.039	.218†	-.003
13. vmPFC													.422**	-.254*	-.105	-.189†	.002	.035	-.057	.012
14. dlPFC														-.112	-.045	-.142	-.168	-.040	.054	.013
15. VS-OFC															492**	432**	-.001	.053	-.042	-.153
16. VS-vmPFC																.257*	.055	.014	-.090	-.043
17. vmPFC-dlPFC																	.054	.057	-.186	-.094
18. AADIS FU																		.694**	.177	.258*
19. SIP FU																			.192	.251*
20. BDI FU																				.070
21. ASRM FU																				

Note. † p <.10; * p < .05; ** p <.01. BAS = Behavioral Activation Scale total score; SR = Sensitivity to Reward score; BDI = Beck Depression Inventory score at scan; ASRM = Altman Self-Rating Mania Scale at scan; AADIS = Adolescent Alcohol and Drug Involvement Scale at scan; Age = Age at scan; Medication = psychotropic medication status at scan; VS = ventral striatum; OFC = orbitofrontal cortex; vmPFC = ventromedial prefrontal cortex; dlPFC = dorsolateral prefrontal cortex; FU = follow-up

Behavioral Results

Exploratory Question 2

Hit rate.

Total mean hit rate (HR) across all trials was .54 (.14) and frequency tables showed 80% of the sample had HRs of .50 or higher. Thus, to maximize inclusion of data in subsequent analyses and considering that the MID sets accuracy at 66%, we set the HR cut-off point at .50. All participants scoring below this cut-off for total HR were excluded from behavioral analyses.

A two-way ANOVA of HRs was conducted with condition (large win, small win, neutral, small loss, large loss) as a within subjects factor and group (SUD, BSD, BSD+SUD, HC) as the between subjects factor (Figure 2). Results revealed no significant group x condition interactions for HRs, $F(10.70, 228.30) = .53$, $p = .89$. One-way ANOVAs revealed no significant main effect for group on HRs, $F(3, 66) = .65$, $p = .59$. However, there was a significant main effect of condition on HRs, $F(3.67, 374.78) = 3.47$, $p = .01$. Bonferroni-adjusted post-hoc tests revealed that participants had significantly higher HRs during large loss trials than during small win and neutral trials (mean differences = .04, ps = .01).

Finally, we examined the associations between HRs and follow-up mood and substance symptoms using Pearson correlations. Depression scores (BDI) at follow-up were correlated negatively with HRs during small loss trials, $r(58) = -.27$, $p = .04$, such that higher HRs were associated with lower depressive symptoms at follow-up. We followed up this significant correlation with linear regression analyses to examine the

effect of HR during small losses as a predictor of BDI scores at follow-up; however, these analyses yielded no significant findings, β = -.15, SE = .13, p = .23.

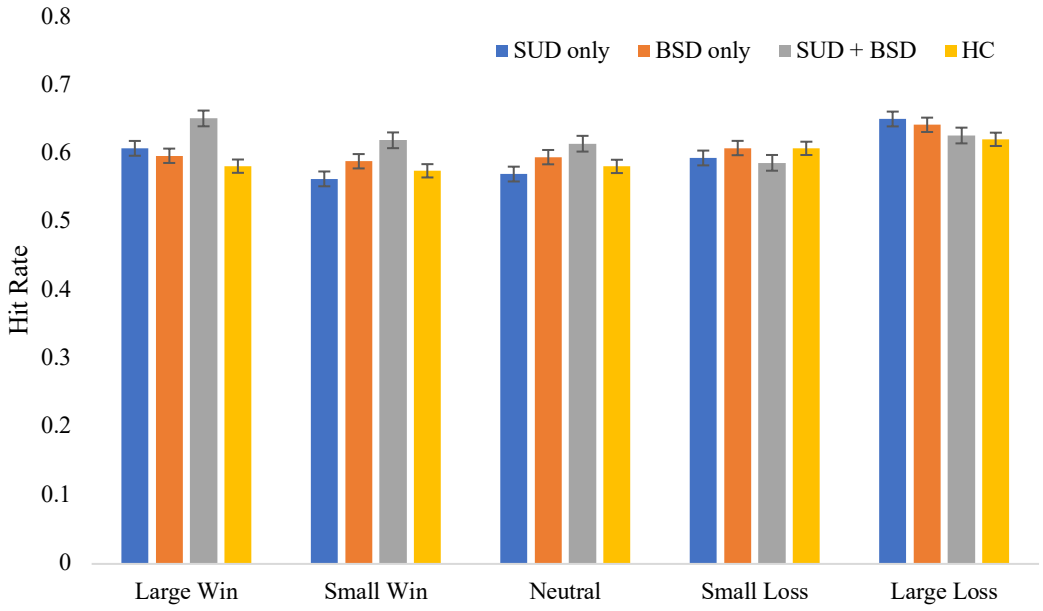

Figure 2. Hit Rates by Group and Condition during MID task.

Reaction time.

A two-way ANOVA of reaction times (RT) was conducted with condition (large win, small win, neutral, small loss, large loss) as the within subjects factor and group (SUD, BSD, BSD+SUD, HC) as the between subjects factor (Figure 3). There were no statistically significant interactions between group and condition for RT, $F(12, 264)$ = 1.37, p = .18. Furthermore, one-way ANOVAs revealed no significant differences in total RT by group, $F(3, 66)$ = .29, p = .83. However, there was a significant effect of condition on RTs, $F(4, 408)$ = 42.18, p <.01. Bonferroni-adjusted post-hoc tests revealed that participants had significantly slower RTs during neutral trials (Win or Lose $0) compared to all other conditions (mean difference Large Win = 14.74, mean difference Small Win = 8.52, mean difference Small Loss = 7.49, mean difference Large Loss = 13.04, all ps <

.01). Additionally, RTs during large wins and losses did not significantly differ from each other; however, RTs were significantly faster during these large win/loss trials compared to their small win/loss counterparts (mean differences = -6.21, -5.56, *p*s < .01).

Finally, we examined the association between RTs and mood and substance symptoms at follow-up. Pearson correlations revealed significant associations only for hypomania (ASRM) scores at follow-up. Total RT, RT during large wins/losses, and RT for neutral trials were associated negatively with ASRM scores at follow-up, *r*s(57) = -.28 - -.29, all *p*s < .05. Thus, faster RTs were associated with higher hypo/mania symptoms at follow-up. Follow-up linear regressions yielded no significant results for total RT predicting ASRM, β = -.07, *SE* = .17, *p* = .61, RT during large wins predicting ASRM, β = -.07, *SE* = .14, *p* = .63, RT during large losses predicting ASRM, β = -.07, *SE* = .14, *p* = .61, or RT during neutral trials predicting ASRM, β = -.08, *SE* = .14, *p* = .58.

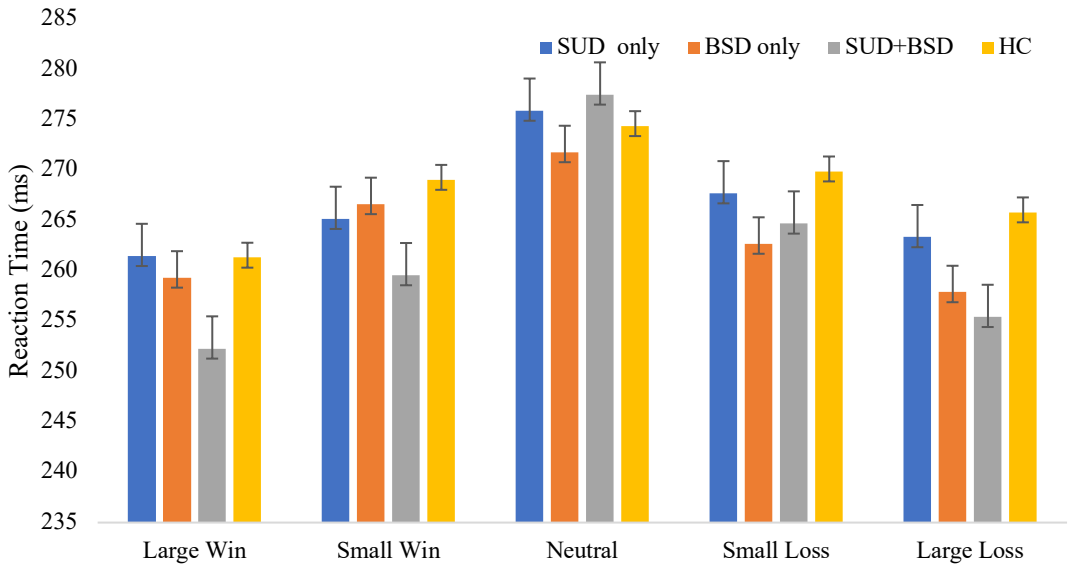

Figure 3. Reaction Times by Group and Condition during MID Task.

Imaging Results

Prospective Analyses (Primary Hypotheses)

The primary study aims were to examine whether activation in primary ROIs (bilateral VS, bilateral OFC, vmPFC, and bilateral dlPFC) during reward anticipation, as well as VS-OFC, VS-vmPFC, and vmPFC-dlPFC connectivity would predict prospective substance use and mood symptoms. We conducted four separate sets of multiple linear regression analyses using MPlus version 7. Each set consisted of activation in each ROI (VS, OFC, vmPFC, and dlPFC) predicting to an outcome (ASRM, BDI, AADIS, and SIP). Similarly, we conducted three sets of analyses for connectivity analyses predictors, in which we included three beta estimates from PPI analyses (VS-OFC, VS-vmPFC, and vmPFC-dlPFC) as independent variables predicting to our four outcomes. For both ROI and connectivity regressions, we included AADIS, ASRM, and BDI scores at time of scan and follow-up time period as covariates in all analyses. In addition to these covariates, we also included age at MRI and BAS total score in analyses predicting mood symptoms, gender and race in analyses predicting substance use symptoms, and medication status at scan in analyses predicting depressive symptoms. This was based on the significant correlations between potential predictors and outcome variables shown in Table 2.

Before performing analyses, we checked that the data met all assumptions for linear regression using visual displays with normal P-P plots of residual vs. predicted values, VIF values, and skewness statistics. The ASRM and AADIS analyses met all assumptions for linear regression. We removed one obvious outlier (+3 SDs above mean) from BDI scores, which significantly improved normality and skew. We also removed

one obvious outlier (+3 SDs above mean) from the SIP data. However, after removing this outlier, the SIP still showed positive skew and heteroskedasticity. Thus, to improve our estimation, we used an MLR estimator in MPlus. All other analyses were conducted with maximum likelihood estimation in MPlus.

ROI activation as predictors of prospective mood symptoms (Hypothesis 1a).

Multiple linear regressions revealed no statistically significant results for activation in the four ROIs predicting subsequent depression (BDI) or hypomania (ASRM). See Supplementary Tables 1 and 2 for results.

Connectivity as predictor of prospective mood symptoms (Hypothesis 1b).

Multiple linear regression revealed no significant results for connectivity in VS-OFC, VS-vmPFC, or vmPFC-dlPFC predicting subsequent depression (BDI) or hypomania (ASRM). See Supplementary Tables 3 and 4 for results.

ROI activation as predictors of prospective substance use (Hypothesis 2a).

Multiple linear regressions revealed no significant results for any of the four ROIs predicting to prospective substance use impairment (SIP; see Supplementary Table 5). Results predicting to subsequent substance use frequency (AADIS) revealed that lower activation in both the dlPFC and the VS was predictive of higher AADIS scores at next follow-up. The vmPFC and OFC were not significant predictors of prospective AADIS scores (see Table 3 and Figures 4 and 5 for detailed results).

Connectivity as predictors of prospective substance use (Hypothesis 2b).

Multiple linear regressions revealed no significant results for connectivity in VS-OFC, VS-vmPFC, or vmPFC-dlPFC predicting subsequent substance use impairment (SIP) or frequency (AADIS) during reward anticipation (see Supplementary Tables 6 and

7 for results). However, because ROI activation in the dlPFC and VS during reward anticipation significantly predicted follow-up AADIS scores, we further probed fronto-striatal connectivity by examining whether connectivity between limbic and prefrontal regions during specific reward anticipation contexts (i.e., salience vs. valence) would differentially predict AADIS scores. Results suggested that vmPFC-dlPFC connectivity during reward anticipation (valence) significantly predicted AADIS scores at follow-up (β = .15, p = .05, SE = .08), but salience did not (β = -.03, p = .81, SE = .13; see Figure 6). Similarly, VS-OFC connectivity during reward anticipation (valence) predicted AADIS at a trend level (β = .14, p = .06, SE = .08), but salience did not (β = -.07, p = .35, SE = .08). There were no significant results for VS-vmPFC connectivity during reward anticipation (valence) predicting AADIS (β = -.07, p = .39, SE = .08) or during salience (β = -.05, p = .52, SE = .08).

Table 3. *Multiple Linear Regression Results for ROI Activation during Reward Anticipation Predicting Subsequent Substance Use Frequency (AADIS; n = 91)*

	Dependent Variable: Adolescent Alcohol and Drug Involvement Scale (AADIS) at follow-up			
	Model 1 (VS)	Model 2 (OFC)	Model 3 (vmPFC)	Model 4 (dlPFC)
Intercept	2.22** (.80)	1.92* (.80)	1.85* (.80)	1.54† (.79)
AADIS at scan	.54** (.08)	.57** (.08)	.58** (.08)	.58** (.08)
ASRM at scan	.03 (.08)	.01 (.08)	.01 (.08)	.01 (.08)
BDI at scan	.11 (.07)	.13 (.08)	.11 (.08)	.12 (.07)
Gender	.01 (.08)	-.01 (.08)	-.00 (.08)	-.01 (.08)
Race	-.14 (.08)	-.12 (.08)	-.12 (.09)	-.09 (.08)
Follow-Up Time	.09 (.08)	.09 (.08)	.06 (.08)	.11 (.08)
VS	-.16* (.08)			
OFC		-.09 (.08)		
vmPFC			-.02 (.07)	
dlPFC				-.19* (.08)
R^2	.54** (.07)	.52** (.07)	.51** (.07)	.54** (.07)

Note. Standardized beta coefficients are displayed, and standard errors are shown in parentheses; **p < .01, *p<.05, †p<.06; AADIS = Adolescent Drug and Alcohol Involvement Scale; ASRM = Altman Self-Rating Mania Scale; BDI = Beck Depression Inventory; Gender (0 = male); Race (0 = White); VS = ventral striatum; OFC = orbitofrontal cortex; vmPFC = ventromedial prefrontal cortex; dlPFC = dorsolateral prefrontal cortex

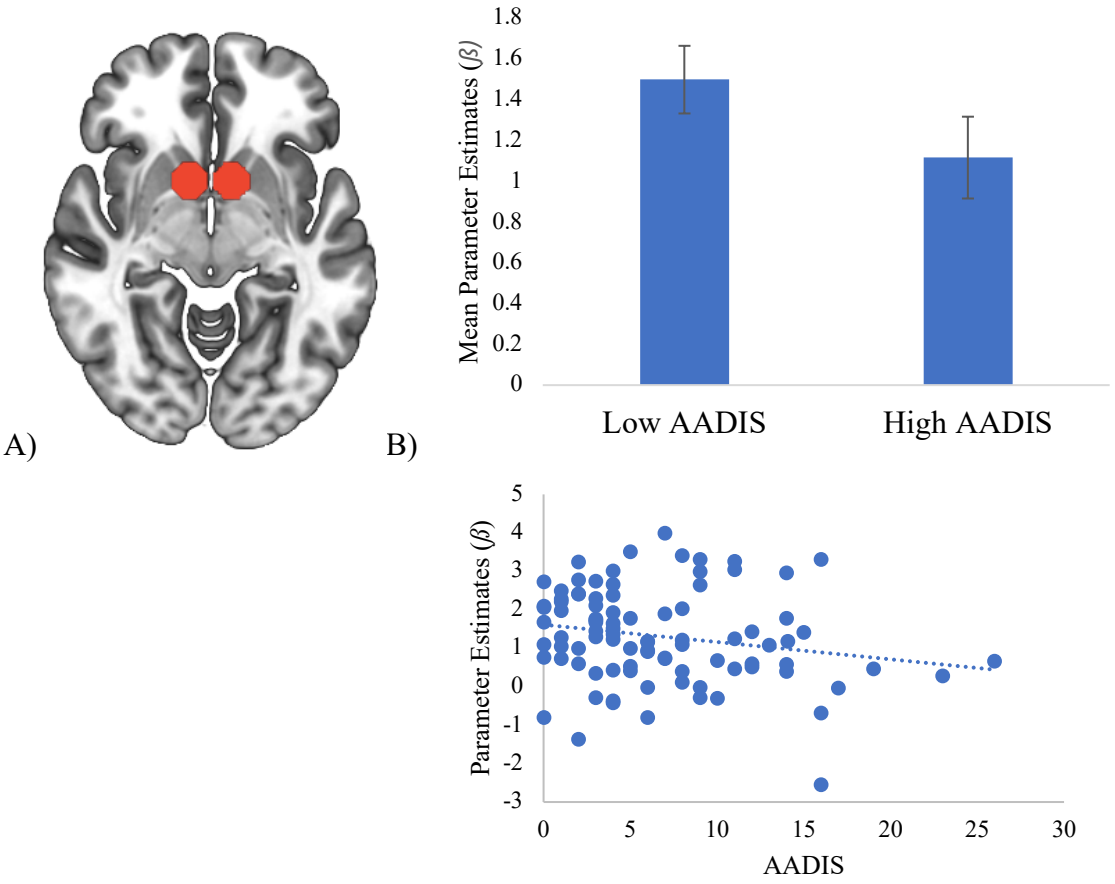

Figure 4. Activation during reward anticipation in the (A) ventral striatum, (B) mean parameter estimates for high and low substance use frequency (AADIS) groups at follow-up, and (C) parameter estimates plotted with follow-up AADIS scores.

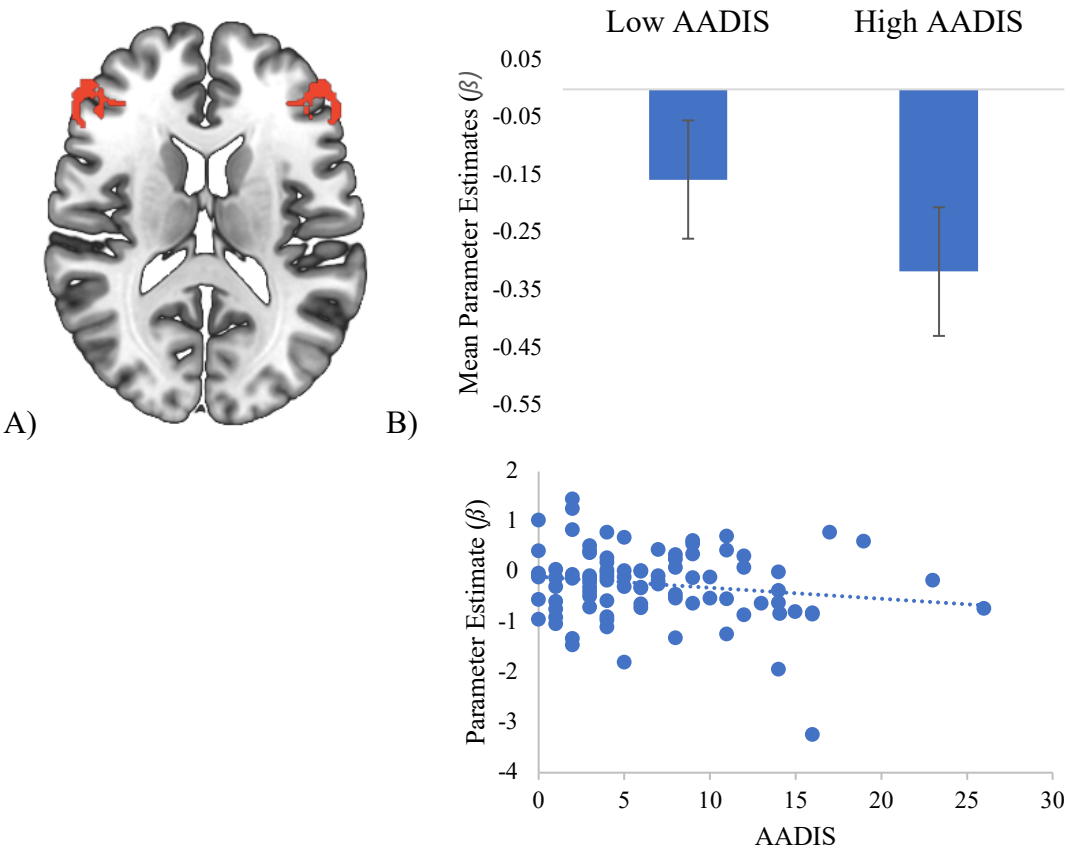

Figure 5. Activation during reward anticipation in the (A) dorsolateral prefrontal cortex, (B) mean parameter estimates for high and low substance use frequency (AADIS) at follow-up, and (C) parameter estimates

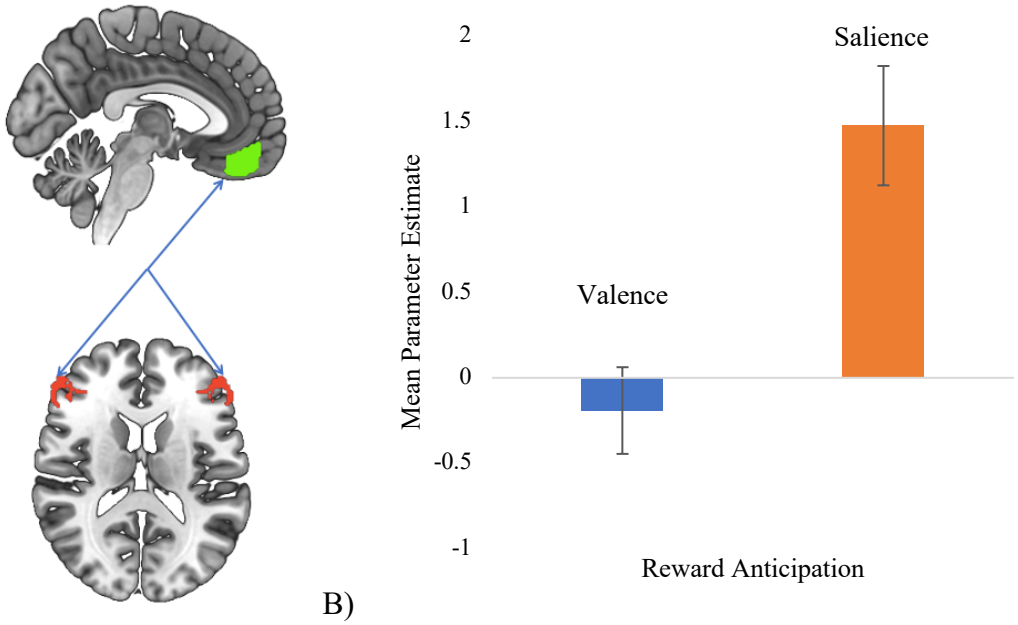

Figure 6. (A) Connectivity between the ventromedial prefrontal cortex (green) and dorsolateral prefrontal cortex (red) during (B) reward anticipation (valence and salience). Error bars represent standard error.

Group Analyses (Exploratory Question 1)

Given the small sample sizes of our individual groups (SUD, BSD, BSD+SUD, and HC), we conducted ANCOVAs on an exploratory basis to assess group differences in neural activation in ROIs and connectivity during reward anticipation. Inasmuch as BAS total score was associated significantly with at least one ROI, we included this as a covariate in ROI analyses, and because race was associated significantly with at least one connectivity parameter estimate, we included it as a covariate in connectivity analyses. We also included AADIS scores at time of scan because analyses suggested that it differed by group. Age at scan and gender were included as covariates to enhance homogeneity in test results. We conducted ANCOVAs to compare BSD, SUD, and HC, in addition to ANCOVAs to compare BSD, SUD, HC, and BSD+SUD. In the event that we found significant group differences, we ran two-way mixed ANCOVAs to determine

the level of reward drove the results (salience; large vs. small vs. neutral). Mean parameter estimates and standard deviations for each diagnostic group is shown in Table 4.

Table 4. *Mean Parameter Estimates and Standard Deviations for ROI Activation and Connectivity*

	Group			
	SUD	BSD	SUD+BSD	HC
OFC	.381(.710)	.460(1.087)	.329(.620)	.234(.461)
VS	1.416(1.364)	1.350(1.480)	1.202(1.039)	1.050(1.006)
vmPFC	.115(.776)	-.102(1.025)	-.047(1.065)	.285(.805)
dlPFC	-.189(.750)	-.122(.650)	-.309(.840)	-.318(.472)
VS-OFC	.038(.879)	-.267(1.153)	.290(.737)	.003(.590)
VS-vmPFC	.498(1.569)	-.399(1.420)	.766(1.721)	-.308(1.561)
vmPFC-dlPFC	.176(.859)	.114(.660)	.104(.949)	-.033(.658)

Note. SUD = Substance Use Disorder; BSD = Bipolar Spectrum Disorder; HC = Healthy Control; OFC = orbitofrontal cortex; VS = ventral striatum; vmPFC = ventromedial prefrontal cortex; dlPFC= dorsolateral prefrontal cortex

ROI analyses (Exploratory Question 1).

First, four ANCOVAs were run to assess the effect of group (SUD, BSD, HC) on reward anticipation activation in the VS, OFC, vmPFC, and dlPFC, controlling for BAS total score, AADIS at scan, age, and gender. Levene's tests of homogeneity of variance indicated that there was homogeneity of variances in all models (ps > .05), except for the OFC (p = .03). Results yielded no significant group differences in any of the ROIs (see Supplementary Table 8).

Second, we modeled the same four ANCOVAS; however, we included our fourth SUD+BSD group (SUD, BSD, HC, SUD+BSD). Levene's tests of homogeneity of variance indicated that there was homogeneity of variances in all models (ps > .05), except for the dlPFC (p = .03) and OFC (marginal p = .05). Similar to our three group

analyses, there were no significant findings for effect of group on reward anticipation activation in any of the ROIs (see Supplementary Table 9).

Connectivity analyses (Exploratory Question 1).

Three ANCOVAs were run to assess the effect of group (SUD, BSD, HC) on connectivity between the VS-OFC, VS-vmPFC, and vmPFC-dlPFC during reward anticipation, controlling for AADIS at scan, age, gender, and race. Levene's tests of homogeneity of variance indicated that there was homogeneity of variances in all models (*p*s > .05). Results yielded no significant group differences for connectivity (see Supplementary Table 10).

Second, we modeled the same three ANCOVAS; however, we included our fourth SUD+BSD group (SUD, BSD, HC, SUD+BSD). Levene's tests of homogeneity of variance indicated that there was homogeneity of variances in all models (*p*s > .05). Similar to our three group analyses, there were no significant group differences for connectivity (see Supplementary Table 11).

Discussion

The current study examined neural reward activation in and connectivity between four regions in the fronto-striatal reward circuit (VS, OFC, vmPFC, and dlPFC) as predictors and/or corollaries of mood and substance use symptoms and disorders, and as possible common mechanisms associated with the co-occurrence of BSDs and SUDs. Results suggested that decreased activation in the VS and dlPFC predicts greater substance use frequency at follow-up. In addition, greater negative connectivity between the vmPFC and dlPFC during high reward valence signals, but not salience signals, also predicted substance use frequency at follow-up. We did not find significant group

differences in activation or connectivity during reward processing, nor did we find that activation or connectivity during reward processing was a significant predictor of mood symptoms. Taken together, the current study suggests that blunted neural responses to monetary rewards in both the reward and cognitive control circuits predict prospective substance use. Furthermore, because changes in fronto-striatal connectivity during changing reward valence contexts also was associated with prospective substance use, the study not only provides evidence for potential dysfunction *within* circuits, but also *between* circuits regulating reward, motivated behavior, and cognitive control as potential mechanisms in the progression of substance use and SUDs.

The current study extends the extant literature in a number of important ways. First, the results from the current study add to the few longitudinal studies that attempt to examine neural reward function as potential *predictors* of future problematic mood and substance use symptoms. Our findings provide evidence that blunted fronto-striatal activation and connectivity are associated with future substance use. Second, to our knowledge, this was the first study that attempts to elucidate common neural mechanisms in BSDs and SUDs by directly comparing individuals with these disorders. Although our findings do not replicate previous research that shows differences in reward-related neural mechanisms are associated with SUDs and BSDs, it is an initial attempt to add to the literature on comorbidity. This is an important emerging field, and the current study highlights the need for larger, longitudinal studies and open science efforts in order to more fully examine the neurodevelopmental trajectories of substance and mood disorders and related psychopathologies.

Our finding that decreased activation in the VS during reward anticipation predicts higher frequency of substance use at next follow-up supports the theory that people who engage in substance use exhibit hyposensitivity in reward regions (Blum et al., 2000). Essentially, people with a blunted reward circuit may seek exogenously what they lack endogenously, and engage in substance use as a way to counteract dysphoria and increase pleasure. It should be noted that although we attempted to control for the number of baseline substance symptoms (i.e., substance use symptoms at time of scan), our sample was not substance-naïve, and thus, the effects of prior substance use on brain function cannot be ruled out. Indeed, there is evidence that suggests that because drugs of abuse carry a high reward value, prolonged use of them causes neuroadaptations in the reward circuit, which results in a "hijacking" of dopaminergic reward regions and disruption in neural regions associated with incentive salience (e.g., VS; Volkow, Fowler, Wang, Swanson, & Telang, 2007). In other words, over time and with prolonged substance use, individuals become "desensitized" to other non-drug related reward cues and have limited resources for non-drug rewards (Berridge & Robinson, 2016).

We also found decreased activation to reward anticipation in the dlPFC predicted future substance use frequency. The dlPFC is a prefrontal brain region involved in behavioral control, such as inhibiting risky choices, and in guiding decisions in the presence of goal-relevant stimuli (i.e. rewards; Banich et al., 2000; MacDonald, Cohen, Stenger, & Carter, 2000). Thus, blunted activation in this region suggests lower recruitment in regions responsible for inhibition during reward-relevant tasks is associated with future risky but pleasurable behaviors that have potential for negative consequences (i.e., substance use). Whereas blunted neural activation in the VS may be

indicative of disruption in incentive sensitization processes as discussed previously, it is possible that blunted activation in the dlPFC may reflect diminished ability for control regions to modulate signals from lower-level reward regions. Indeed, follow-up analyses involving connectivity between the dlPFC and vmPFC suggest that disrupted connectivity during reward valence between these regions was associated with future substance use. As previously discussed, the vmPFC is a critical "relay" center where signals from the reward circuit (VS) and control circuit (dlPFC) converge. Although directionality of signals cannot be fully ascertained using PPI analyses, one possibility is that an abnormal weighting of signals disrupts adequate mediation between these circuits and that this contributes to higher tendency to engage in substance use.

Because our sample did include some individuals who already had engaged in substance use and some who had a diagnosed SUD, our results suggest that decreased activation in the striatum is associated with *worsening course* or progression of substance use and SUDs. Future work is needed in substance-naïve samples to fully assess whether reward hyposensitivity in the striatum is indeed a *pre-existent* risk factor for SUDs. However, in supplementary regression analyses, removing participants who had a history of SUD and/or BSD yielded similar findings. Although these analyses were underpowered, these results show preliminary support that blunted reward processing may not only be associated with worsening course of substance use, but that it may also indicate that hyposensitivity to secondary rewards within regions involved in reward processing and behavioral control may serve as a *pre-existent* risk factor for prospective substance use. Of course, more work is necessary using larger, substance-naïve samples to fully assess this hypothesis.

Additionally, because we found that substance use frequency was associated with changes in connectivity during reward valence, and not reward salience, future research involving reward processing should focus on how valence and salience processes are differentially associated with mood and substance use disorders. Indeed, there is evidence that the VS and OFC are involved in salience and valence, respectively, and reflects different processes related to reward learning (Jensen et al., 2007). As these reward processes are disrupted in individuals with BSDs and SUDs, it is important that future work considers the differential roles of both salience and valence mechanisms as they relate to risk for both disorders.

Despite these significant findings, our analyses yielded null results for ROI activation and connectivity predicting future mood symptoms, and activation and connectivity did not significantly distinguish individuals with BSD, SUD, comorbid BSDs and SUDs, and healthy participants. Although there is evidence for differential patterns of reward processing and fronto-striatal connectivity among individuals with SUDs, BSDs, and healthy participants, as well as differences based on mood state (Alloy, Nusslock, et al., 2015; Mason, O'Sullivan, Bentall, & El-Deredy, 2012; Phillips & Swartz, 2014), our study likely was underpowered to capture these differences. Although the majority of the effect sizes in this study were small, we did see medium effect sizes for activation in the vmPFC and VS-vmPFC connectivity during reward anticipation as predictors of group differences. However, due to uneven and small group sizes, interpretation of these effect sizes is limited; larger samples are needed. It is curious that we did not find any results for reward-related brain function as a predictor of future mood symptoms. This may have occurred for a number of reasons. First, the psychometric

properties of our mood symptom measures may have influenced our null findings. For example, the ASRM is brief and provides minimal coverage of the full spectrum of hypomanic symptoms. Additionally, although evidence suggests that it is highly correlated with clinician ratings (Altman et al., 2001), there is the possibility for participants to misinterpret certain items. Finally, because our follow-up was relatively long (M = 8 months), we may not have been able to capture more acute changes in mood symptoms following the time of scanning. This highlights the possibility that reward-related neural activity is a more robust predictor of substance use than mood symptoms.

It is important to note that we were limited by our fMRI task design in examining responsivity only to monetary rewards, and not primary or other secondary rewards. Using monetary rewards for this study was ideal in a number of ways because their value is not influenced by bodily states as in primary rewards, and monetary rewards have been shown consistently to be dysregulated in individuals with SUDs and BSDs (Lutz & Widmer, 2014). However, any discussion of motivated behavior is incomplete without consideration of social rewards, as humans are inherently social beings. Furthermore, social reward processing also is disrupted in SUDs and BSDs (Dutra, Cunningham, Kober, & Gruber, 2015; Preller et al., 2014; Tobler et al., 2016). A recent meta-analysis by Gu et al. (2019) found support for the common-currency hypothesis; that is, common brain regions (namely the VS, ventral tegmental area, anterior insula, and supplementary motor area) are involved in both monetary and social reward anticipation processes. Similarly, a recent review suggests that different types of rewards (money, social, food) activate reward regions (specifically the VS and vmPFC) in a similar manner (for review see Smith & Delgado, 2015). Thus, an important future direction is to understand if there

are similar neural representations for both monetary and social rewards involved in SUDs and BSDs. Understanding the role of social reward processing in these disorders may have particular significance for the development of interventions, as BSDs are known to be associated with social rhythm disruption (for review see Alloy, Nusslock, et al., 2015) and social reward experience has been associated with the development of drug addiction (for review see Beloate & Coolen, 2017).

Another limitation was our study sample. For example, we recruited from a non-treatment seeking, college sample, and although there were occurrences of mood and substance use disorders, it may not have captured the entire breadth of illness severity. Indeed, many participants had less severe forms of BSDs (i.e. cyclothymia, BPNOS), and it is unclear if we would find the same extent of neural reward dysfunction in these individuals as much of the positive findings in the extant literature are on individuals with more severe BSDs (i.e. BPI, BPII; Abler, Greenhouse, Ongur, Walter, & Heckers, 2008; Bermpohl et al., 2010; Caseras, Lawrence, Murphy, Wise, & Phillips, 2013). Furthermore, both psychotropic medications and drugs of abuse cause neuroadaptations to neural circuits, which may influence brain function. Because our groups were not consistent in who had histories of medication or substance use, our ability to detect group differences may have been limited.

Although we did not find support for neural indices as predictors of future mood symptoms, it is worthwhile to point out our significant behavioral findings. We found that higher accuracy (hit rate; HR) during small loss trials was correlated significantly with lower depression scores at follow-up, and that faster reaction times (RT) across trials (except small rewards/losses) were correlated significantly with higher hypomania scores

at follow-up. These significant associations are important for a number of reasons. First, these findings corroborate previous research that suggests that RT and HR measures may be useful in understanding how cognitive difficulties (i.e., attention, processing speed) in people with psychiatric illnesses may be associated with mood symptoms and psychological distress (Fleck, Sax, & Strakowski, 2001; Gale, Harris, & Deary, 2016). Second, when it comes to reward-related processes specifically, the fact that lower prospective depression and higher prospective hypomania were associated with better accuracy and faster RT, respectively, during specific reward contexts, further suggests that mood symptoms are associated with dysfunction in reward-related processes. Thus, these results add to the extant literature that suggests BSDs are associated with increased "urgency" in reward-related contexts, which leads to difficulty in inhibiting prepotent responses, inaccurate reward-related decision making, and impulsivity (Chase et al., 2018).

Finally, we did not find support for our hypotheses that co-morbidity between BSDs and SUDs may be driven by common shared neural mechanisms. Although the current study was underpowered to detect group differences, we emphasize the importance of classifying psychiatric disorders based on dimensions of neurobiological measures and processes through an RDoC approach in order to inform future work on comorbidity (Insel et al., 2010). Specifically, by considering methods to examine how neural reward processing (a positive valence system) is a dimension that crosses disorders, more theoretically-driven questions related to understanding comorbidity can be addressed. For example, as it pertains to reward processing in BSDs and SUDs, a multifinality/equifinality perspective may be best (Nusslock & Alloy, 2017). That is,

whereas multifinality suggests that similar mechanisms (i.e. blunted fronto-striatal connectivity) can result in different outcomes (e.g., BSDs and SUDs), equifinality suggests that the same outcome (e.g., SUD) can result from different mechanisms (hyper vs. hypoactivity in the reward circuit; see Chapter 3 for further review). In this same vein, reward processing is complex, and although research points to specific neural regions involved in reward anticipation, our imaging analysis approach was not sensitive enough to fully characterize neural representations of reward within these regions, and therefore, this limits conclusions regarding shared neural mechanisms. Indeed, using more sensitive approaches, such as multi-voxel pattern analysis (MVPA), would allow us to better examine the relationships between voxels within a given region, and thus, more fully ascertain how different components of reward processing relate to different outcomes. Indeed, researchers have used MVPA successfully and other pattern-based approaches to identify distinct neural processes despite similar fMRI activity within the same neuroanatomical regions (Kahnt et al., 2014; Woo et al., 2014). Thus, using these more sensitive approaches would allow us to examine if more nuanced components of reward processing (i.e. salience vs valence) in BSDs and SUDs are actually characterized by similar or different neural representations within the fronto-striatal reward circuit.

Conclusions and Future Directions

Although SUDs are very common in individuals with mental health problems, a recent survey suggests that individuals with BSDs have a higher rate of SUDs compared to any other mental health disorder (Grant et al., 2004). Despite this, there has been minimal work on the underlying neurobiological mechanisms that contribute to the course, maintenance, and etiology of co-occurring BSDs and SUDs. It has been theorized

that these disorders frequently co-occur due to dysfunction in shared mechanisms that underlie reward, motivated behavior, and impulsivity (Swann, 2010). Thus, the development of treatments that target these shared etiological pathways may be particularly beneficial for individuals with BSD and SUD comorbidity. Although results from the current study do not support our hypotheses related to common pathways within these individuals, it does provide insight into potential factors that relate to worsening course for substance use. Specifically, we highlight the need for new theoretical approaches (i.e. multifinality/equifinality, multivariate imaging methods) in examining reward-related processes across highly co-occurring disorders. Whereas it is abundantly clear that both SUDs and BSDs are characterized by dysfunction in the neural reward and control circuits, the current state of the literature would benefit from longitudinal, within-subjects designs, larger samples, and increased data sharing among researchers.

CHAPTER 2

SUPPLEMENTARY MATERIAL

Additional Analyses Related to Primary Hypotheses

As our sample consisted of participants who had already been diagnosed with both SUDs and BSDs, we ran additional analyses to explore whether activation and connectivity within and between the VS, OFC, vmPFC, and dlPFC would prospectively predict mood and substance symptoms when excluding these participants from analyses. By removing these participants, we attempted to address the question of whether neural reward dysfunction may constitute a pre-existent risk factor for prospective substance use and mood symptoms. Similar to our primary analyses, for both ROI and connectivity regressions, we included AADIS, ASRM, and BDI scores at time of scan and follow-up time period as covariates in all analyses. In addition to these covariates, we also included age at MRI and BAS total score in analyses predicting mood symptoms, gender and race in analyses predicting substance use symptoms, and medication status at scan in analyses predicting depressive symptoms.

Nineteen participants who were included in our primary prospective analyses predicting to mood symptoms had been diagnosed with a BSD, and thus, we removed these participants from supplementary analyses. Thus, our sample consisted of 69 participants without a history of BSD at time of scan. Multiple linear regression analyses yielded no significant findings for activation in the VS, OFC, vmPFC, or dlPFC during reward anticipation, or connectivity between VS-OFC, VS-vmPFC, or vmPFC-dlPFC

during reward anticipation predicting to either BDI or ASRM scores at follow-up (all *ß*s = -.09 - .14, all *p*s > .12).

Thirty participants who were included in our primary prospective analyses predicting to substance use symptoms had been diagnosed with a SUD, and thus, we removed these participants from supplementary analyses. Thus, our sample consisted of 60 participants without a history of SUD at time of scan. Multiple linear regression analyses yielded no significant findings for activation in the VS, OFC, vmPFC, or dlPFC during reward anticipation, or connectivity between VS-OFC, VS-vmPFC, or vmPFC-dlPFC during reward anticipation predicting to SIP scores at follow-up (all *ß*s = -.15 - .14, all *p*s > .16).

Finally, we re-ran analyses predicting AADIS scores (substance use frequency) at follow-up. Results confirmed our primary analyses that lower activation in the VS and dlPFC predicted higher AADIS scores at follow-up (*ß* = -.28, p < .01; *ß* = -.35, *p* < .01, respectively). Additionally, we found that activation in the OFC predicted higher AADIS scores at a trend-level of significance (*ß* = -.21, *p* = .06). Analyses yielded no significant findings for activation in the vmPFC, or connectivity between VS-OFC, VS-vmPFC, or vmPFC-dlPFC predicting AADIS scores at follow-up (all *ß*s = -.12 - .03, *p*s > .26).

Supplementary Results

Table 5. *Multiple Linear Regression Results for ROI Activation during Reward Anticipation Predicting Subsequent Depressive Symptoms (BDI; n = 88)*

	Dependent Variable: Beck Depression Inventory (BDI) at follow-up			
	Model 1 (VS)	Model 2 (OFC)	Model 3 (vmPFC)	Model 4 (dlPFC)
Intercept	1.66 (1.17)	1.78 (1.16)	1.82 (1.17)	1.93 (1.20)
AADIS at MRI	-.10 (.09)	-.11 (.09)	-.11 (.09)	-.11 (.09)
ASRM at MRI	.10 (.09)	.10 (.09)	.11 (.09)	.11 (.09)
BDI at MRI	.65** (.07)	.64** (.07)	.64** (.07)	.65** (.07)
BAS total	-.17* (.08)	-.18* (.08)	-.18* (.08)	-.18* (.08)
Medication status	.08 (.08)	.07 (.08)	.08 (.08)	.07 (.08)
Follow-Up Time	.12 (.08)	.11 (.08)	.12 (.08)	.11 (.08)
Age at scan	.01 (.08)	.01 (.08)	.01 (.08)	.00 (.08)
VS	.04 (.08)			
OFC		.05 (.08)		
vmPFC			.04 (.08)	
dlPFC				.05 (.08)
R^2	.48** (.08)	.48** (.08)	.48** (.08)	.48** (.08)

Note. Standardized beta coefficients are displayed, and standard errors are shown in parentheses; **p < .01, *p<.05, †p<.06; AADIS = Adolescent Drug and Alcohol Involvement Scale; ASRM = Altman Self-Rating Mania Scale; BDI = Beck Depression Inventory; BAS = Behavioral Activation Scale; Medication Status = taking psychotropic medication within 2 weeks of scan; VS = ventral striatum; OFC = orbitofrontal cortex; vmPFC = ventromedial prefrontal cortex; dlPFC = dorsolateral prefrontal cortex

Table 6. *Multiple Linear Regression Results for ROI Activation during Reward Anticipation Predicting Subsequent Hypomanic Symptoms (ASRM; n = 89)*

	Dependent Variable: Altman Self Rating Mania Scale (ASRM) at follow-up			
	Model 1 (VS)	Model 2 (OFC)	Model 3 (vmPFC)	Model 4 (dlPFC)
Intercept	-.35 (1.28)	-.22 (1.27)	-.28 (1.28)	-.21 (1.32)
AADIS at scan	.16 (.10)	.15 (.09)	.14 (.09)	.14 (.09)
ASRM at scan	.42** (.09)	.43** (.09)	.43** (.09)	.43** (.09)
BDI at scan	.01 (.09)	.01 (.09)	.01 (.09)	.01 (.09)
BAS total	.19* (.09)	.18* (.09)	.19* (.09)	.19* (.09)
Follow-Up Time	.03 (.09)	.04 (.09)	.04 (.09)	.04 (.09)
Age at scan	-.11 (.09)	-.11 (.09)	-.11 (.09)	-.11 (.09)
VS	.06 (.09)			
OFC		.02 (.09)		
vmPFC			-.03 (.09)	
dlPFC				.00 (.09)
R^2	.36** (.08)	.36** (.08)	.36** (.08)	.36** (.08)

Note. Standardized beta coefficients are displayed, and standard errors are shown in parentheses; **p < .01, *p<.05, †p<.06; AADIS = Adolescent Drug and Alcohol Involvement Scale; ASRM = Altman Self-Rating Mania Scale; BDI = Beck Depression Inventory; BAS = Behavioral Activation Scale; Medication Status = taking psychotropic medication within 2 weeks of scan; VS = ventral striatum; OFC = orbitofrontal cortex; vmPFC = ventromedial prefrontal cortex; dlPFC = dorsolateral prefrontal cortex

Table 7. *Multiple Linear Regression Results for Connectivity during Reward Anticipation Predicting Subsequent Depressive Symptoms (BDI; n = 85)*

	Dependent Variable: Beck Depression Inventory (BDI) at follow-up		
	Model 1 (VS-OFC)	Model 2 (VS-vmPFC)	Model 3 (vmPFC-dlPFC)
Intercept	1.66 (1.19)	1.70 (1.19)	1.85 (1.20)
AADIS at scan	-.10 (.09)	-.12 (.09)	-.09 (.09)
ASRM at scan	.11 (.09)	.12 (.09)	.11 (.09)
BDI at scan	.63** (.07)	.64** (.07)	.62** (.07)
BAS total	-.18* (.08)	-.18* (.08)	.19* (.08)
Medication status	.08 (.08)	.08 (.08)	.09 (.08)
Follow-Up Time	.10 (.09)	.12 (.08)	.10 (.08)
Age at scan	.03 (.08)	.02 (.09)	.02 (.08)
VS-OFC	-.03 (.08)		
VS-vmPFC		.04 (.09)	
vmPFC-dlPFC			-.08 (.08)
R^2	.47** (.08)	.47** (.08)	.48** (.08)

Note. Standardized beta coefficients are displayed, and standard errors are shown in parentheses; **p < .01, *p<.05, †p<.06; AADIS = Adolescent Drug and Alcohol Involvement Scale; ASRM = Altman Self-Rating Mania Scale; BDI = Beck Depression Inventory; BAS = Behavioral Activation Scale; Medication Status = taking psychotropic medication within 2 weeks of scan; VS-OFC = ventral striatum – orbitofrontal cortex connectivity; VS-vmPFC = ventral striatum – ventromedial prefrontal cortex connectivity; vmPFC-dlPFC = ventromedial prefrontal cortex – dorsolateral prefrontal cortex connectivity

Table 8. *Multiple Linear Regression Results for Connectivity during Reward Anticipation Predicting Subsequent Hypomanic Symptoms (ASRM; n = 86)*

	Dependent Variable: Altman Self Rating Mania Scale (ASRM) at follow-up		
	Model 1 (VS-OFC)	Model 2 (VS-vmPFC)	Model 3 (vmPFC-dlPFC)
Intercept	-.20 (1.29)	-.15 (1.30)	-.16 (1.31)
AADIS at scan	.15 (.10)	.13 (.10)	.14 (.10)
ASRM at scan	.43** (.09)	.44** (.09)	.43** (.09)
BDI at scan	.01 (.09)	.01 (.09)	.01 (.09)
BAS total	.17* (.09)	.18* (.09)	.18* (.09)
Follow-Up Time	.02 (.09)	.04 (.09)	.03 (.09)
Age at scan	-.10 (.09)	-.11 (.09)	-.11 (.09)
VS-OFC	-.06 (.09)		
VS-vmPFC		.03 (.10)	
vmPFC-dlPFC			-.01 (.09)
R^2	.36** (.08)	.36** (.08)	.36** (.08)

Note. Standardized beta coefficients are displayed, and standard errors are shown in parentheses; **p < .01, *p<.05, †p<.06; AADIS = Adolescent Drug and Alcohol Involvement Scale; ASRM = Altman Self-Rating Mania Scale; BDI = Beck Depression Inventory; BAS = Behavioral Activation Scale; VS-OFC = ventral striatum – orbitofrontal cortex connectivity; VS-vmPFC = ventral striatum – ventromedial prefrontal cortex connectivity; vmPFC-dlPFC = ventromedial prefrontal cortex – dorsolateral prefrontal cortex connectivity.

Table 9. *Multiple Linear Regression Results for ROI Activation during Reward Anticipation Predicting Subsequent Substance Use Impairment (SIP; n = 90)*

	Dependent Variable: Short Inventory of Problems (SIP) at follow-up			
	Model 1 (VS)	Model 2 (OFC)	Model 3 (vmPFC)	Model 4 (dlPFC)
Intercept	4.35** (.54)	4.27** (.54)	4.28** (.54)	4.19** (.54)
AADIS at scan	.60** (.09)	.62** (.09)	.62** (.09)	.63** (.09)
ASRM at scan	.17† (.09)	.15 (.08)	.15 (.08)	.15 (.09)
BDI at scan	.19 (.10)	.20* (.10)	.19† (.10)	.19† (.10)
Gender	-.05 (.09)	-.06 (.09)	-.06 (.09)	-.06 (.09)
Race	.07 (.07)	.08 (.08)	.08 (.08)	.10 (.08)
Follow-Up Time	-.02 (.13)	-.02 (.13)	-.04 (.12)	-.01 (.13)
VS	-.09 (.07)			
OFC		-.05 (.07)		
vmPFC			.04 (.08)	
dlPFC				-.09 (.07)
R^2	.53** (.08)	.53** (.08)	.53** (.08)	.53** (.08)

Note. Standardized beta coefficients are displayed, and standard errors are shown in parentheses; **p < .01, *p<.05, †p<.06; AADIS = Adolescent Drug and Alcohol Involvement Scale; ASRM = Altman Self-Rating Mania Scale; BDI = Beck Depression Inventory; Gender (0 = male); Race (0 = White); VS = ventral striatum; OFC = orbitofrontal cortex; vmPFC = ventromedial prefrontal cortex; dlPFC = dorsolateral prefrontal cortex

Table 10. *Multiple Linear Regression Results for Connectivity during Reward Anticipation Predicting Subsequent Substance Use Impairment (SIP; n = 87)*

	Dependent Variable: Short Inventory of Problems (SIP) at follow-up		
	Model 1 (VS-OFC)	Model 2 (VS-vmPFC)	Model 3 (vmPFC-dlPFC)
Intercept	4.29** (.52)	4.23** (.53)	4.22** (.53)
AADIS at scan	.62** (.09)	.62** (.09)	.62** (.09)
ASRM at scan	.14 (.08)	.15 (.09)	.15 (.08)
BDI at scan	.20 (.10)	.19 (.11)	.20 (.11)
Gender	-.07 (.09)	-.05 (.09)	-.06 (.09)
Race	.05 (.08)	.07 (.08)	.07 (.08)
Follow-Up Time	-.05 (.12)	-.03 (.13)	-.03 (.13)
VS-OFC	-.08 (.07)		
VS-vmPFC		.01 (.10)	
vmPFC-dlPFC			.01
R^2	.53** (.09)	.53** (.09)	.53** (.09)

Note. Standardized beta coefficients are displayed, and standard errors are shown in parentheses; **p < .01, *p<.05, †p<.06; AADIS = Adolescent Drug and Alcohol Involvement Scale; ASRM = Altman Self-Rating Mania Scale; BDI = Beck Depression Inventory; VS-OFC = ventral striatum – orbitofrontal cortex connectivity; VS-vmPFC = ventral striatum – ventromedial prefrontal cortex connectivity; vmPFC-dlPFC = ventromedial prefrontal cortex – dorsolateral prefrontal cortex connectivity

Table 11. *Multiple Linear Regression Results for Connectivity during Reward Anticipation Predicting Subsequent Substance Use Frequency (AADIS; n = 88)*

	Dependent Variable: Adolescent Alcohol and Drug Involvement Scale (AADIS) at follow-up		
	Model 1 (VS-OFC)	Model 2 (VS-vmPFC)	Model 3 (vmPFC-dlPFC)
Intercept	.49* (.22)	.46* (.83)	.45* (.22)
AADIS at scan	.59** (.08)	.61** (.08)	.59** (.08)
ASRM at scan	.04 (.08)	.04 (.08)	.05 (.08)
BDI at scan	.13 (.08)	.12 (.08)	.12 (.08)
Gender	-.01 (.08)	<.01 (.08)	.01 (.08)
Race	-.15 (.09)	-.14 (.09)	-.13 (.09)
Follow-Up Time	.02 (.08)	.02 (.08)	.03 (.08)
VS-OFC	-.07 (.08)		
VS-vmPFC		-.07 (.08)	
vmPFC-dlPFC			-.02 (.08)
R^2	.50** (.08)	.50** (.08)	.50** (.08)

Note. Standardized beta coefficients are displayed, and standard errors are shown in parentheses; **p < .01, *p<.05, †p<.06; AADIS = Adolescent Drug and Alcohol Involvement Scale; ASRM = Altman Self-Rating Mania Scale; BDI = Beck Depression Inventory; VS-OFC = ventral striatum – orbitofrontal cortex connectivity; VS-vmPFC = ventral striatum – ventromedial prefrontal cortex connectivity; vmPFC-dlPFC = ventromedial prefrontal cortex – dorsolateral prefrontal cortex connectivity

Table 12. *ANCOVA Results for Activation in ROIs during Reward Anticipation for Three Groups (BSD, SUD, HC); df = 2, 52.*

	MS	*F*	*p*	*Partial* η^2
Ventral Striatum				
Corrected Model	1.37	.83	.55	.09
Intercept	5.64	3.42	.07	.06
BAS total	.90	.54	.46	.01
AADIS at scan	2.82	1.71	.20	.03
Age at scan	1.84	1.12	.30	.02
Gender	1.08	.66	.42	.01
Group	1.80	1.09	.40	.04
Orbitofrontal Cortex				
Corrected Model	.30	.52	.79	.06
Intercept	.11	.19	.68	<.01
BAS total	.10	.17	.68	<.01
AADIS at scan	.03	.05	.83	<.01
Age at scan	<.01	<.01	.95	.00
Gender	1.01	1.72	.20	.03
Group	.31	.52	.60	.02
Ventromedial PFC				
Corrected Model	1.13	1.53	.19	.15
Intercept	.87	1.18	.28	.02
BAS total	.01	.01	.92	.00
AADIS at scan	.06	.08	.79	<.01
Age at scan	.96	1.30	.26	.02
Gender	1.82	2.47	.12	.05
Group	1.20	1.63	.21	.06
Dorsolateral PFC				
Corrected Model	.45	1.15	.35	.12
Intercept	.84	2.15	.15	.04
BAS total	.01	.02	.90	.00
AADIS at scan	.26	.67	.42	.01
Age at scan	1.20	3.08	.09	.06
Gender	.68	1.73	.19	.03
Group	.30	.76	.47	.03

Note. BSD = Bipolar Spectrum Disorder; SUD = Substance Use Disorder; HC = Healthy Control; BAS = Behavioral Activation Scale; AADIS = Adolescent Alcohol and Drug Involvement Scale score

Table 13. *ANCOVA Results for Activation in ROIs during Reward Anticipation for Four Groups (BSD, SUD, HC, BSD+SUD); df = 3, 62.*

	MS	*F*	*p*	*Partial* η^2
Ventral Striatum				
Corrected Model	.99	.63	.73	.07
Intercept	6.24	3.95	.05	.06
BAS total	1.02	.64	.43	.01
AADIS at scan	2.97	1.88	.18	.03
Age at scan	1.95	1.23	.27	.02
Gender	.39	.25	.62	<.01
Group	1.24	.79	.51	.04
Orbitofrontal Cortex				
Corrected Model	.18	.32	.94	.04
Intercept	.30	.53	.47	.01
BAS total	.13	.23	.63	<.01
AADIS at scan	.17	.31	.58	.01
Age at scan	.02	.03	.86	.00
Gender	.41	.72	.40	.01
Group	.24	.42	.74	.02
Ventromedial PFC				
Corrected Model	.72	.87	.54	.09
Intercept	.50	.60	.44	.01
BAS total	<.01	<.01	.95	.00
AADIS at scan	<.01	<.01	.96	.00
Age at scan	.73	.88	.35	.01
Gender	.46	.55	.46	.01
Group	.94	1.14	.34	.05
Dorsolateral PFC				
Corrected Model	.23	.49	.84	.05
Intercept	1.00	2.17	.15	.03
BAS total	.15	.32	.58	.01
AADIS at scan	.14	.31	.58	.01
Age at scan	.64	1.40	.24	.02
Gender	.04	.08	.78	<.01
Group	.22	.48	.70	.02

Note. BSD = Bipolar Spectrum Disorder; SUD = Substance Use Disorder; HC = Healthy Control; BAS = Behavioral Activation Scale; AADIS = Adolescent Alcohol and Drug Involvement Scale score

Table 14. *ANCOVA Results for Connectivity during Reward Anticipation for Three Groups (BSD, SUD, HC); df = 2, 50.*

	MS	*F*	*p*	*Partial* η^2
VS-OFC				
Corrected Model	.82	1.10	.37	.12
Intercept	.90	1.21	.28	.02
AADIS at scan	.23	.31	.58	.01
Age at scan	1.01	1.36	.25	.03
Gender	1.15	1.54	.22	.03
Race	.49	.66	.42	.01
Group	.24	.32	.73	.01
VS-vmPFC				
Corrected Model	2.76	1.11	.37	.12
Intercept	1.14	.46	.50	.01
AADIS at scan	.28	.11	.74	<.01
Age at scan	1.90	.77	.39	.02
Gender	1.75	.70	.41	.01
Race	2.59	1.05	.31	.02
Group	1.43	1.43	.25	.05
vmPFC-dlPFC				
Corrected Model	.91	1.77	.13	.18
Intercept	.11	.21	.65	<.01
AADIS at scan	.17	.33	.57	.01
Age at scan	.29	.57	.46	.01
Gender	.83	1.62	.21	.03
Race	1.50	2.93	.09	.06
Group	.16	.32	.73	.01

Note. BSD = Bipolar Spectrum Disorder; SUD = Substance Use Disorder; HC = Healthy Control; VS-OFC = ventral striatum – orbitofrontal cortex; VS-vmPFC = ventral striatum – ventromedial prefrontal cortex; vmPFC-dlPFC = ventromedial prefrontal cortex – dorsolateral prefrontal cortex; AADIS = Adolescent Alcohol and Drug Involvement Scale score

Table 15. *ANCOVA Results for Connectivity during Reward Anticipation for Four Groups (BSD, SUD, BSD+SUD, HC); df = 3, 59.*

	MS	*F*	*p*	*Partial* η^2
VS-OFC				
Corrected Model	.98	1.40	.22	.14
Intercept	.69	.99	.32	.02
AADIS at scan	.10	.14	.71	<.01
Age at scan	1.35	1.94	.17	.03
Gender	2.08	2.99	.09	.05
Race	.92	1.33	.25	.02
Group	.55	.79	.50	.04
VS-vmPFC				
Corrected Model	3.89	1.58	.16	.16
Intercept	1.57	.64	.43	.01
AADIS at scan	1.21	.49	.49	.01
Age at scan	3.65	1.48	.23	.03
Gender	.67	.27	.60	.01
Race	7.28	2.95	.09	.05
Group	4.16	1.69	.18	.08
vmPFC-dlPFC				
Corrected Model	.68	1.17	.33	.12
Intercept	.05	08	.77	<.01
AADIS at scan	.04	.08	.79	<.01
Age at scan	<.01	.00	.99	.00
Gender	.31	.54	.47	.01
Race	2.10	3.60	.06	.06
Group	.11	.19	.90	.01

Note. BSD = Bipolar Spectrum Disorder; SUD = Substance Use Disorder; HC = Healthy Control; VS-OFC = ventral striatum – orbitofrontal cortex; VS-vmPFC = ventral striatum – ventromedial prefrontal cortex; vmPFC-dlPFC = ventromedial prefrontal cortex – dorsolateral prefrontal cortex; AADIS = Adolescent Alcohol and Drug Involvement Scale score

CHAPTER 3

ASSOCIATED LITERATURE REVIEW

Introduction

Reward sensitivity, the level of one's approach motivation and responsiveness towards goals and rewards, is associated with the onset and course of bipolar spectrum disorders (BSDs; Alloy, Bender, et al., 2012; Alloy, Urošević, et al., 2012; Nusslock et al., 2012) and substance use disorders (SUDs; Alloy et al., 2009; Dawe, Gullo, & Loxton, 2004; Dawe & Loxton, 2004). Thus, it is not surprising that these two disorders frequently co-occur (Conway, Compton, Stinson, & Grant, 2006); SUDs are present in over a third of people diagnosed with BSDs (Merikangas et al., 2011). Although BSDs are known to be associated with reward hypersensitivity (Alloy, Nusslock, & Boland, 2015; Johnson, Edge, Holmes, & Carver, 2012; Nusslock & Alloy, 2017), there is debate regarding whether SUDs arise from reward hypo- or hypersensitivity (Nusslock & Alloy, 2017). Furthermore, few studies have examined reward processing as a trait level risk factor for these disorders. Identification of neural mechanisms that pre-exist and/or constitute a trait-level vulnerability would help inform our understanding of the onset and course of BSDs and SUDs, and may help clarify why they so highly co-occur.

There are several potential explanations for the high co-occurrence of BSDs and SUDs; 1) substance use (SU) occurs as part of the bipolar syndrome as individuals with BSDs engage in risky and impulsive behaviors, including SU, 2) SU may be an attempt by individuals with BSDs to self-medicate, 3) SU may cause BSDs, and 4) BSDs and SUDs share common risk factors (for review see Strakowski & Delbello, 2000). Relevant

to this latter possibility, there are a number of common risk factors for both BSDs and SUDs, including exposure to stressful life events and genetic factors, but in this review, we examine the extent to which dysfunction in neural reward processing constitutes a risk factor for both BSDs and SUDs. Specifically, in one prospective study examining bipolar diagnosis and SU problems over a follow-up time period, self-reported reward sensitivity at baseline was associated with prospective BSDs and SU, and even partially explained the prospective comorbid relationship between BSDs and SUDs (Alloy et al., 2009). Although these associations were found using self-report measures of reward sensitivity, this adds to the theory that abnormalities in reward sensitivity comprise a common risk factor for both BSDs and SUDs. Thus, the current review investigates evidence for this theory by examining the neural mechanisms underlying this potential shared risk factor.

In the current review, we aim to examine the degree to which dysfunction in the neural reward circuit represents a pre-existing and/or trait-level vulnerability to BSDs and SUDs, by reviewing literature that implements the following types of study designs: 1) truly prospective studies predicting initial onset of SUDs[1], 2) familial risk studies that examine unaffected offspring or first-degree relatives of family members with a BSD or SUD, and 3) studies that examine neural reward processing in individuals with a BSD or SUD who are not currently in an episode of the disorder (e.g., remitted or euthymic). Thus, this review aims to identify profiles of reward processing that may represent a pre-existing vulnerability, as well as a trait-level corollary of BSDs and SUDs. We conclude by offering a synthesis of the findings in both BSDs and SUDs, and present a potential

[1] The literature review yielded no prospective studies of neural reward function as measured by the MID task predicting to BSD onset.

integrated theoretical model of neural reward processing in BSDs and SUDs. Limitations of the extant literature and future directions also are discussed.

Neural Substrates of Reward Sensitivity

The dopaminergic fronto-striatal reward circuit is a vital component of the human brain. A range of brain regions form the reward circuit; these areas process both internal and external reward-related stimuli, predict the probability of future reward based on past events, and are associated with incentive salience, associative reward learning, and positively-valenced emotions, all of which contribute to the regulation of motivated and goal-directed behaviors (Haber & Knutson, 2010; Schultz & Dickinson, 2000). Two primary regions of this circuit are the ventral striatum (VS) and orbitofrontal cortex (OFC). The VS may be involved primarily in encoding and anticipating rewards (Dillon et al., 2008; Knutson, Taylor, Kaufman, Peterson, & Glover, 2005), although some have found elevated VS activity in the presence of reward receipt (Seymour, Daw, Dayan, Singer, & Dolan, 2007). The OFC primarily is implicated in assessing both the value and probability of reward receipt (McDannald, Lucantonio, Burke, Niv, & Schoenbaum, 2011). A meta-analysis of human neuroimaging studies confirmed the predominant roles of the VS and OFC in reward anticipation and reward consumption, respectively (Diekhof, Kaps, Falkai, & Gruber, 2012). Other regions that comprise this circuit and interact via dopaminergic pathways are the ventral tegmental area (VTA), substantia nigra, anterior cingulate cortex (ACC), amygdala, ventral pallidum, dorsal striatum (DS), raphe nuclei, lateral habenula nucleus, and more frontal regions of the prefrontal cortex including dorso- and ventrolateral regions (dlPFC/vlPFC; Haber & Knutson, 2010). Together, they form the fronto-striatal reward circuit, which is facilitated by dopamine

transmission, and aids in reinforcement signaling and learning (reviewed in Haber & Knutson, 2010). Importantly, this circuit regulates anticipatory and consummatory reward processing to help drive motivation, goal-striving, and approach behavior in the presence of reward-related cues (Berridge & Robinson, 1998, 2003).

Researchers can study the reward circuit experimentally by observing brain responses during presentation (or omission) of reward stimuli. Secondary rewards are those that are not inherently valuable but are associated with pleasurable consequences, such as money, and often are used experimentally such as in the Monetary Incentive Delay (MID) task (for review see Lutz & Widmer, 2014). The MID presents the participant with an opportunity to either gain or lose rewards (e.g., $0.00, $0.50, $5.00) based on how quickly they respond to a target, and thus, can be used to study distinct phases of reward processing such as anticipation (period of the task when they are awaiting feedback of reward or loss) versus consumption (period of the task when they have received feedback of reward or loss; Knutson, Adams, Fong, & Hommer, 2001). Another form of a monetary reward task asks participants to guess whether the value of a card will be greater than or equal to, or less than 5, where correct guesses result in winning money on reward trials and avoiding losing money on loss trials (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000). This task also has differentiated neural activity to different phases of reward processing (e.g. anticipation vs. consumption) reliably in both healthy individuals and those with various psychopathologies (Forbes et al., 2009; Knutson et al., 2001). Thus, the MID and card guessing tasks are superior tools for capturing differences in reward processing among groups (e.g. BSDs and SUDs) with known abnormalities in neural reward processing.

Reward and Bipolar Spectrum Disorders

There is considerable theoretical and empirical support for a prominent role of dopaminergic fronto-striatal reward circuit dysfunction in BSDs. The Behavioral Approach System (BAS)/reward hypersensitivity model of BSDs posits that excessive activation or deactivation of the reward system results in the extreme mood and behavior swings that are characteristic of BSDs (for reviews see Alloy et al., 2015; Alloy, Olino, Freed, & Nusslock, 2016; Depue & Iacono, 1989; Depue, Krauss, & Spoont, 1987; Johnson, 2005; Johnson, Edge, Holmes, & Carver, 2012). The reward system responds to certain triggering events (e.g., events related to excessive goal-striving or rewards that activate it, and events related to definite failures or losses that deactivate it) as well as internal (e.g. expectation of meeting a goal) or external (e.g., receiving an award) stimuli. Someone with a hypersensitive BAS/reward system would react to these stimuli more strongly than others. Reward hypersensitive individuals may experience strong positive emotions or engage in risky, yet pleasurable, behaviors when in a state of reward system activation. On the other hand, these same individuals may experience strong negative emotions and extreme anhedonia when in a state of reward system deactivation. Indeed, there is a large body of research that supports the reward hypersensitivity theory across multiple methods. People with BSDs have been shown consistently to have elevated self-reported reward sensitivity and reward-relevant personality traits (Alloy et al., 2008; Johnson et al., 2012; Johnson, Eisner, & Carver, 2009; Meyer, Johnson, & Winters, 2001). Behavioral tasks involving reward sensitivity (i.e., delayed gratification of rewards, increased positive affect after receiving rewards) differentiate people with BSDs or with manic symptoms from those without (Johnson, Ruggero, & Carver, 2005; Swann,

Lijffijt, Lane, Steinberg, & Moeller, 2009). Finally, reward hypersensitivity is a key predictor of the initial onset and course of BSDs (for reviews see Alloy et al., 2015; Alloy et al., 2016; Nusslock & Alloy, 2017).

There is additional support for the reward hypersensitivity model of BSDs in the neurobiological and neurophysiological literatures (for reviews see Alloy et al., 2015; Nusslock & Alloy, 2017; Phillips & Swartz, 2014). Elevated left frontal EEG activity has been linked to increased approach behavior and response bias towards reward-relevant stimuli, as well as greater self-reported reward sensitivity (for review see Coan & Allen, 2004). Elevated left frontal EEG activity has been seen both in people who are prone to hypomania and people with a bipolar diagnosis (Harmon-Jones et al., 2008, 2002; Mason et al., 2012), and is associated with conversion to more severe forms of BSD (Nusslock, Alloy, et al., 2012). Structural MRI imaging has provided evidence for abnormalities in prefrontal and striatal volumes in people with or at-risk for BSDs (López-Larson, DelBello, Zimmerman, Schwiers, & Strakowski, 2002; McDonald et al., 2004; Strakowski et al., 2002). Functional MRI (fMRI) studies using reward-based tasks also have demonstrated that consummatory and anticipatory reward processing abnormalities may be differentially associated with BPI versus BPII (Caseras et al., 2013). Additionally, mania and depression both have been associated with higher activation in reward regions (Abler et al., 2008; Bermpohl et al., 2010).

In parallel, the dopamine hypothesis of BSDs suggests that hyperdopaminergia, along with an elevated reward processing network, underlies the illness (Ashok et al., 2017). This hypothesis came about through investigation of the similarities between mania and the effects of amphetamine, along with the anti-manic actions of anti-

dopaminergic drugs (M. M. Singh, 1970). Functional imaging evidence supports the dopamine hypothesis, as elevated BOLD signals occur in the striatum and prefrontal cortex shortly after presentation of reward cues (Schott et al., 2008). These regions are rich in dopaminergic projections, and this BOLD activation is presumably related to dopamine transmission via projections from the VTA to the VS and prefrontal cortical areas (Schott et al., 2008). Although the dopamine hypothesis historically has focused on the manic phase of BSDs, new hypotheses suggest a differential role for increased striatal dopaminergic receptors in mania, and for increased striatal dopamine transporters during depression, providing support for hyperdopaminergia theory across mood states (for review see Ashok et al., 2017). However, this hypothesis does not fully explain dopamine functioning during remitted or euthymic phases of BSDs.

Although there is compelling evidence that BSDs are associated with elevated activity in the fronto-striatal reward circuit, conclusions regarding whether neural reward hypersensitivity does indeed constitute a trait vulnerability to BSDs are limited. First, there remains conflicting evidence regarding whether individuals with current mania consistently have elevated VS activity during reward tasks. Although across studies, BSD patients (euthymic or in a manic state) had elevated prefrontal responses to reward, findings differed with regards to whether BSD patients had reduced activation or showed no difference from healthy controls in the VS (Abler et al., 2008; Bermpohl et al., 2010; Nusslock, Almeida, et al., 2012; Singh et al., 2013). Most of the studies discussed have been cross-sectional, and thus, limit conclusions regarding the role of neural reward processing during the course and onset of BSDs. Additionally, most of the extant literature includes BSD samples that have been medicated with antidopaminergic

medications. Dopamine transmission plays a key role in reward processes in the brain, and thus, medications that regulate this system may lead to lasting neural adaptations within the reward circuit. Thus, in order to draw conclusions regarding profiles of reward processing as pre-existing vulnerabilities to BSDs, there is a need to study reward processing using longitudinal approaches, prior to the onset of BSDs, in which individuals have not received pharmacological interventions.

Reward and Substance Use Disorders

Whereas most of the literature suggests that BSDs are associated with fronto-striatal hypersensitivity (Alloy et al., 2015, 2016; Nusslock & Alloy, 2017), the literature concerning reward function and addiction is guided by two opposing theoretical models. The Reward Deficiency Model of addiction (Blum et al., 2000; Bowirrat & Oscar-Berman, 2005; Volkow, Fowler, & Wang, 2003) posits that all addictive drugs activate reward regions through increasing dopamine, but that once addicted, drugs trigger smaller increases in dopamine. This system becomes less stimulated by both drug and non-drug related cues (e.g., everyday stimuli). This effect also can be seen in neural circuits involved in emotion regulation (e.g., amygdala), as people try to cope with the negative emotions and dysphoria related to withdrawal by increasing approach behaviors towards drugs (e.g., increased substance-seeking; Volkow, Koob, & McLellan, 2016). For example, people who have relapsed on cocaine show significantly lower activation in the bilateral striatum across trials on a reward learning task, compared to their abstinent counterparts (Stewart et al., 2014). Additionally, findings from positron emission tomography (PET) studies fairly consistently demonstrate down-regulation of dopamine in people with substance addictions (for review see Volkow et al., 2003). Thus, according

to the Reward Deficiency Model, substance-seeking behaviors arise from an individual's attempts to compensate for the lack of recruitment in the reward circuit and inability to experience pleasure from rewards (Blum et al., 2000; Bowirrat & Oscar-Berman, 2005; Volkow et al., 2003).

On the other hand, the Reward Hypersensitivity Model postulates that people with high reward sensitivity engage in excessive approach behavior to attain rewards that can lead to risky behaviors with pleasurable consequences like SU (Alloy et al., 2009; Dawe et al., 2004; Dawe & Loxton, 2004; Kambouropoulos & Staiger, 2004). In line with this perspective, researchers have found that high reward sensitivity as assessed by self-report and behavioral measures predict SUDs, and distinguish between heavy and light drinkers (for review see Nusslock & Alloy, 2017). Additionally, the inability to delay gratification is associated with increased risk for addiction, and evidence from imaging studies suggests hyperactivity in the VS underlies a preference for immediate over delayed rewards (Hariri et al., 2006). Similar to neurophysiological findings in BSDs, there also is support for elevated left frontal EEG cortical activity in SUDs. This pattern was found in nicotine-dependent individuals when presented with a reward cue to smoke (Zinser, Fiore, Davidson, & Baker, 1999). Substances of abuse are themselves rewarding, and studies examining neural response to drug cues consistently have demonstrated hyperactivation in the reward circuit (for review see Leyton & Vezina, 2013). Furthermore, drugs stimulate reward regions (e.g., VS), which over time become hypersensitized, leading to increased approach motivation towards substances (Baskin-Sommers & Foti, 2015; Di Chiara et al., 2004). This hyper-responsivity in the reward

circuit may underlie a propensity to be motivated towards rewarding and pleasurable stimuli such as drugs (McClure, Laibson, Loewenstein, & Cohen, 2004).

A possible explanation for these inconsistencies in the literature on reward and SUDs is that reward processing may be different depending on phase of addiction. For example, it is thought that attenuated responses in the VS and DS during monetary reward processing may be particularly prevalent during remission, whereas more robust responses in these regions reflect active addiction (Balodis & Potenza, 2015). However, current addiction phase did not seem to impact findings from a recent meta-analysis demonstrating that SUDs are associated with an overall blunted response during monetary reward processing (Luijten et al., 2017). Regardless, given the neural adaptations that substances of abuse may create in the reward circuit and the considerable discrepancies in the functional imaging literature, it is important to consider substance-naïve samples when addressing questions related to neural reward functioning and SUD risk (Hommer, Bjork, & Gilman, 2011). Given the considerable research on underlying reward processes once addiction has set in, there is a substantial gap in our knowledge of how reward processing impacts the initial onset of SUDs, and thus, we still do not fully understand whether reward hyper- or hyposensitivity comprises a pre-existing risk factor for SUDs.

Methods

This review focused on functional activation in reward-related neural circuits during processing of monetary rewards. We chose to focus on monetary rewards because they have been shown consistently to be dysregulated in individuals with SUDs and BSDs, and tasks of monetary reward are reliable in evoking neural responses (Knutson,

Westdorp, Kaiser, & Hommer, 2000; Lutz & Widmer, 2014). Thus, in order to be included in the review, articles had to report on studies implementing the MID task or the card-guessing task. We decided to limit our search to only the MID or card-guessing tasks because they are thought to reflect a relatively pure method of analyzing discrete reward consumption and anticipation processes (Knutson et al., 2001). As the aim of the current review was to focus solely on whether reward circuit dysfunction during reward processing constitutes a vulnerability or risk factor for SUDs and BSDs, articles reporting on current in-episode samples were excluded. Given the small body of literature, we included a variety of study designs that could assess trait-level risk for SUDs and BSDs. Studies could be longitudinal and prospective (e.g., using fMRI to prospectively predict first onset of SUD or BSD), or cross-sectional (e.g., remitted/euthymic samples compared to healthy controls or to in-episode individuals). Additionally, to expand our review of pre-existing reward-related risk factors, we also included studies that examined samples of "at-risk" individuals based on having a first-degree relative with either a SUD or BSD, but no current diagnosis themselves. Search terms included combinations of the following entered into PsycInfo and PubMed: reward, reward sensitivity, MRI, fMRI, functional imaging, monetary reward, monetary incentive delay, MID, vulnerability, risk, risk factor, bipolar, mania, hypomania, manic, hypomanic, substance, substance use, drug, drug use, cocaine, marijuana, cannabis, alcohol, nicotine, abuse, dependence, familial risk, onset, euthymic, remitted, remission, offspring. Additional articles were collected by manual searches of the reference sections of the retrieved articles.

Results

The searches in PsycInfo and PubMed yielded 238 unique articles. Articles related to remitted/euthymic samples were excluded if they were part of a treatment trial as the treatment is considered a confounding variable. Two hundred and nine articles were identified as clearly not meeting eligibility requirements. Figure 1 depicts a flow diagram of the number of studies identified for the current review, the number excluded and reasons for exclusion, as well as numbers included. The remaining 29 articles were read in full to determine their eligibility. There were no articles that used fMRI measures of monetary reward processing to prospectively predict to onset of BSDs. Thus, 29 articles met eligibility for this systematic review: 4 on familial risk for BSDs, 7 on euthymic BSDs, 9 prospective studies of SUDs, 7 on familial risk for SUDs, and 2 on remitted SUDs (see Tables 5 and 6).

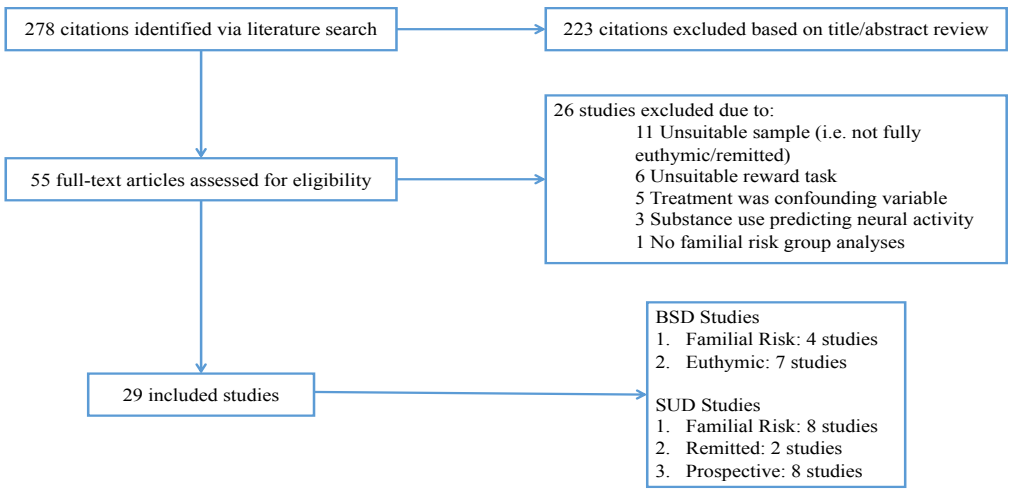

Figure 7. Flowchart of Study Selection.

Neural Reward Dysfunction as a Familial Risk Factor for BSDs

The literature search revealed no prospective studies examining neural reward function as a predictor of first onset of BSDs/(hypo)mania. However, given the high genetic risk associated with BSDs, studies that utilize a high-risk design by examining neural reward function in unaffected offspring or first degree relatives of people with BSDs can inform our understanding of the neural reward dysfunction that may mediate genetic and/or familial risk for the development of BSDs. The literature search revealed four studies that utilized functional MRI during the MID task to examine reward processing in offspring of individuals with BSDs.

Singh and colleagues (2014) were the first to study activation and connectivity in the reward circuit during a reward processing task in young offspring of at least one biological parent with BPI, compared to offspring of parents with no Axis I psychopathology, who also had no second-degree relative with a history of an Axis I disorder. Singh et al. (2014) found that compared to children of healthy parents, offspring of a BPI parent exhibited less activation in the pregenual cingulate cortex during loss anticipation vs. reward anticipation (the opposite was found in the healthy control group) on an MID task. Additionally, offspring of BPI parents had greater activation in the left lateral OFC during reward consumption (versus successfully avoiding losing money) and greater activation in this region during reward consumption compared to healthy control offspring. Results from functional connectivity analyses revealed that within the fronto-striatal circuit, children with parents with BPI had less connectivity between the pregenual cingulate and the right vlPFC during reward anticipation compared to loss anticipation. When compared to children of unaffected parents, offspring of BPI parents

exhibited greater connectivity between the pregenual cingulate and the right vlPFC during loss compared to reward anticipation. No significant functional connectivity differences were observed during consumption of loss or reward. Thus, this study was the first to demonstrate that there is indeed aberrant reward function in healthy offspring of parents with BSDs. Overall, high-risk children exhibited decreased activation in and connectivity between regions associated with reward-related decision making during loss anticipation, and greater prefrontal (OFC) activations to reward consumption. Findings from this study suggest that neural deficits in regions important for processes related to decision-making, delaying gratification, and regulating emotion may comprise an endophenotype of BPI.

Three additional studies used the card-guessing task to examine neural responses to reward or loss consumption (Acuff et al., 2019; Manelis et al., 2016; Soehner et al., 2016) in high-risk offspring. This specific task required participants to make a guess about whether the number on a card would be higher or lower than 5, so the authors included analyses related to a "decision making" trial, which included phases where participants had to make a decision regarding the number on a card as well as receipt of feedback for rewards or losses (Bebko et al., 2014). Because a decision-making trial strays from how the classic MID task is analyzed, and also because reward-related decision making may involve different neural circuits, it is important to interpret the results from these papers with this in mind. Manelis et al. (2016) found that compared to offspring of non-BSD parents or HC, offspring of parents with BSDs had greater functional connectivity between the VS and right vlPFC during control trials relative to receipt of rewards or losses, which partly supports findings from Singh et al. (2014).

Furthermore, these findings remained significant when participants who were on medication or had other psychiatric diagnoses were removed from analyses. However, these findings were not supported by Soehner et al. (2016), who found elevated VS connectivity with the left posterior insula and vlPFC during reward consumption in offspring of parents with BSDs, although this finding may have been primarily driven by the effect of sleep duration, which also was tested in this study. In the third, and most recent study, unaffected offspring of parents with BSDs had lower functional connectivity between the right VS and left ACC to loss consumption, but greater functional connectivity between the right pars orbitalis and bilateral OFC to reward consumption, while controlling for other non-BSD diagnoses, medications, and mood symptoms (Acuff et al., 2019).

These contradictory findings obtained using different reward tasks demonstrates the complexity of reward processing. Studies utilizing varying functional reward tasks may not be directly comparable, as they may tap into different processes that are differentially associated with regions within the fronto-striatal reward circuit. Thus, Singh et al.'s (2014) findings are in need of replication. The Bipolar Illness Onset study is a large longitudinal study that is currently underway, which will use the MID to study reward function in offspring of parents with BSDs (Kessing et al., 2017). Thus, these findings may be replicated in the future; however, currently we are limited in the conclusions we can draw regarding neural reward processing in familial high-risk samples.

A further limitation of Singh et al.'s (2014) study is the fact that people who have a familial history of BSDs also are at higher risk for developing non-BSD

psychopathology as well as BSDs (Birmaher et al., 2009; Goldstein et al., 2010), and so, it is important to consider this as a confounding factor when designing high-risk offspring studies. Manelis et al. (2016) attempted to address this issue by comparing offspring of parents with a history of BPI or BPII, offspring of parents with non-BSD psychopathology (e.g., unipolar depression), and offspring of parents with no psychopathology. By including these three groups, the authors were able to separate what may be unique risk factors for BSDs versus other types of psychopathology. Additionally, many of the offspring had a history of other psychopathology and either were on medication or had a history of taking psychiatric medication. These factors all can impact reward-related brain function, and thus, it is important to study these processes in offspring without histories of any psychopathology, and without medication history.

A further limitation of these few offspring studies is that they all had modest sample sizes, and thus, may be underpowered. Their cross-sectional designs also do not allow for an examination of developmental trajectories of reward processing. Indeed, the offspring in these studies included a very wide age range (e.g., 8 to 15 years) during a time period when rapid brain changes are occurring in the fronto-striatal circuit. Additionally, cross-sectional designs without information about which offspring go on to develop BSDs do not allow us to examine what profiles of reward function constitute a risk or resilience factor for BSDs. Longitudinal studies are needed to address both these issues.

Neural Reward Dysfunction as a Trait Risk Factor for BSDs

Compared to the literature on high-risk offspring, there have been more studies examining reward function in individuals who have been diagnosed with BSDs, but are not currently in a depressed or (hypo)manic episode. Seven studies examined reward processing during an fMRI MID task in remitted BSD patients. Examining neural responses to rewards in individuals who have a BSD, but are euthymic or in a period of "remission" can tell us whether reward-related brain function constitutes more of a persistent, trait-like factor for BSDs, rather than a specific profile that is present only during extreme mood states (e.g., depression vs. mania). A review of these studies, however, reveals mixed findings regarding whether euthymic individuals have hyper- or hypo-sensitivity in reward regions during the MID.

In the first study to examine neural activity during reward processing in euthymic BSDs, Nusslock et al. (2012) used the card-guessing task to compare 21 remitted individuals with BPI to healthy controls. Results revealed that euthymic BPI patients had increased activation in the right VS and right OFC to reward anticipation compared to loss anticipation and to healthy controls. Exploratory whole brain analyses revealed a cluster of activation in the left-lateral OFC during reward anticipation in euthymic individuals. All findings were specific to the anticipation phase of the task. Another study by Caseras et al. (2013) utilized a similar card-guessing paradigm in 32 euthymic BPI or BPII individuals compared to 20 healthy controls. They found increased VS activity during reward anticipation in euthymic BPII individuals, and increased VS activity during positive outcomes in euthymic BPI individuals. Whole brain analyses revealed BPII individuals had increased left vlPFC and superior temporal cortex activation

compared to BPI and controls, and increased bilateral caudate nuclei and left dlPFC activation than controls. Although there were differences among findings between these two studies, they generally support the reward hypersensitivity model of BSDs. Differences in findings between outcome phases, as well as between groups (specifically BPI and BPII), may be explained by the fact that there were differences in how the card guessing tasks were administered. For example, in Caseras et al. (2013), participants were not informed that their payment for the study was dependent on them performing well on the task.

There are other studies on euthymic BSDs that support the reward hyposensitivity perspective. Yip et al. (2015) were the first to examine reward processing in a sample of euthymic BSD individuals who were entirely psychiatric medication naïve. Twenty patients with either BPII or BPNOS, who were remitted from a depressive or hypomanic episode, were compared to 20 healthy controls during a MID task. Findings revealed that euthymic BSD patients had decreased activation in the right DS during reward and loss anticipation. There were no significant findings in the VS. Their findings remained significant when they excluded seven participants who had a history of substance abuse. Thus, Yip et al. (2015) found reward hyposensitivity particularly during anticipation of rewards and losses in a sample of BSD patients who were medication naïve. Additionally, this sample was relatively young, and thus, effects from experience of prolonged BSD illness are unlikely. Another study by Schreiter et al. (2016) also supports the reward hyposensitivity perspective on BSDs. They found that BSD patients in remission from a mood episode for at least five months had decreased activation in the left and right VS during reward anticipation. Furthermore, psychophysiological

interaction (PPI) analyses revealed that the BSD group had decreased connectivity between the left VS and anterior PFC during reward anticipation. Of note, this study was the first to examine functional connectivity on the MID task in BSDs.

Further studies provide mixed findings that either provide evidence for both heightened and blunted activity in the reward circuit during the processing of monetary rewards, or do not provide sufficient evidence to support either perspective. Dutra et al. (2015) used a monetary and a social incentive delay task to compare euthymic BPI individuals who had not experienced a mood episode in at least one month to healthy controls. Additionally, they excluded participants who had substance abuse or dependence in the past six months. Whole brain analyses revealed that healthy controls had greater activation than remitted BSDs in the OFC, bilateral occipital cortex, and bilateral inferior frontal gyri to both monetary and social reward anticipation. On the other hand, region of interest (ROI) and whole brain analyses demonstrated that BSD patients had increased nucleus accumbens (NAcc) activation during monetary and social reward consumption. In a follow up study using the same sample, the authors probed the significant findings for elevated VS activation during reward consumption with functional connectivity analyses (Dutra, Man, Kober, Cunningham, & Gruber, 2017b). They found increased connectivity between the left VS and left OFC and between the bilateral VS and left amygdala to reward consumption, but decreased connectivity between the right VS and medial PFC when expected rewards were omitted in BSD participants. Thus, Dutra and colleagues' (2015, 2017) findings provide mixed evidence for both reward hypo- and hyper-activation during different stages of reward anticipation and consumption. Finally, Kollman et al. (2017) used a non-traditional MID task; they

implemented a paradigm that just measured reward anticipation (Kirsch et al., 2003). They compared euthymic BPI individuals who had no history of comorbidities (e.g., substance use disorders) and who were free from all psychiatric medication at the time of the scan to healthy controls. The only finding was increased activation in the ACC, a region important for emotion regulation, to reward anticipation in the BSD group compared to healthy controls. Thus, this last study does not provide strong support for either hypo- or hyper-activation of the reward circuit in people with remitted BSDs.

Numerous factors may explain the discrepant findings regarding the profile of reward dysfunction that characterizes a trait-level vulnerability for BSDs as defined by being present in individuals who have a BSD diagnosis, but are not currently experiencing a mood episode. Thus, all of the results discussed in this section must be interpreted in the context of these limitations. First and foremost, all of the studies discussed above have small to modest sample sizes, and thus, are lacking in sufficient power to detect smaller effects. Second, the majority of these studies included individuals who either were currently on mood stabilizers or other psychiatric medications, or had a history of being on medication. Many psychiatric medications, particularly antipsychotics, act on the dopaminergic system and can impact functioning in the fronto-striatal reward circuit. Although some studies attempted to limit the possible influence of these medications by either making sure participants were free from medications for a specified period of time or by running additional analyses that excluded participants on current medication, a history of psychiatric medication use still may impact findings (Caseras et al., 2013; Kollmann et al., 2017). Indeed, the one study that recruited mood stabilizer and antipsychotic naïve patients is not without limitations (Yip et al., 2015).

Despite the importance of studying individuals without medication confounds, this also meant that their sample was younger and at the beginning of their BSD illness, and they also tended to have less severe forms of BSDs that did not reach the stage of requiring medication treatment. Thus, the sample characteristics from studies examining medication naïve patients are different from other studies that recruit mainly individuals with BPI disorder, the most severe form, and may not be directly comparable.

In their medication naïve sample, Yip et al. (2015) found blunted activation in the DS to reward anticipation, and this finding held when they removed participants with a history of substance abuse. Indeed, the authors state that the DS has an important function in SUDs, and this blunted activation has been shown in the addiction literature. A history of substance abuse is another confounding factor in many of these studies. Like certain psychiatric medications, substances of abuse act on the dopaminergic reward circuit and can leave lasting effects in the form of neural adaptations. Thus, it also is important, and difficult, to recruit participants with no history of SU. Some researchers try to control for this confound by only including individuals who have been free from SUDs for a specified period of time; however, even these studies report hyper- and hypo-sensitivity (Dutra et al., 2015, 2017b; Nusslock, Alloy, et al., 2012; Yip et al., 2015). The one study that specifically recruited individuals with no other comorbidities (except anxiety disorders) yielded no differences between their BSD group and healthy controls in reward regions during the MID task. When patients with other comorbidities are included, like SUDs, which most of these studies do, the findings are not specific to BSDs. Thus, to fully highlight the profile of reward processing risk specific to BSDs, it's important to recruit patients without other confounding disorders. At the same time, given the high

rates of comorbidities in BSDs, this will be difficult to accomplish and may have limited generalizability (Conway et al., 2006).

Although studying euthymic BSD individuals helps examine questions about whether reward dysfunction is a trait vulnerability, this group is not ideal for determining what actually underlies a pre-existing risk factor for BSDs. Indeed, inherent in the description of euthymic individuals is that many have residual symptoms of depression. All of the studies had cut-offs greater than zero for their euthymic participants on measures of current depression and mania. Thus, we cannot rule out current residual mood symptoms as confounding the results, particularly those that found BSDs were associated with reward hypoactivity, as this profile is also seen in individuals with depression (Hägele et al., 2015). To fully elucidate the underlying neural mechanisms of BSDs, it is crucial to conduct longitudinal studies with individuals who have not yet developed BSDs, who have no psychiatric comorbidities, and who are free of medications to fully control for all of these potential confounding variables.

Summary of Findings from Neuroimaging Literature on BSD

In sum, there are conflicting findings that support both reward hyper- and hypo-sensitivity in BSDs across both offspring and remitted studies. However, trends seem to emerge when one considers the results in the context of processing type (anticipation vs. consumption) and valence (reward vs. loss). For example, the majority of the results across studies suggest that decreased fronto-striatal connectivity is associated with loss consumption, whereas increased fronto-striatal connectivity is associated with reward consumption. The most contradictory findings occur in the reward and loss anticipation analyses. For example, whereas it appears that unaffected offspring of parents with BSDs

exhibit blunted activation in the pregenual cingulate (a region that has important connections to both frontal and striatal regions in the reward circuit), and decreased connectivity between this region and frontal regions during anticipation trials, in studies examining euthymic individuals, we see both blunted and heightened activation in the striatum and frontal regions during anticipation. These discrepancies suggest that a number of factors can confound results related to reward processing. For example, prolonged illness itself, psychotropic medication, and comorbidities all may be confounding variables and a reason why the results are mixed. Additionally, it may not be possible to directly compare bipolar offspring and euthymic studies because of the differences in developmental periods between samples (offspring studies include youth, whereas euthymic studies include adults). Regardless, it appears that differences in connectivity between striatal regions responsible for motivation, emotion regulation, and reward value and frontal areas responsible for inhibitory control may underlie a vulnerability to BSDs, and that this connectivity may undergo normative and disease-specific (e.g., medication use, illness course, comorbidities) changes across development.

Neural Reward Dysfunction as a Familial Risk Factor for SUDs

Data from epidemiological studies suggest that individuals with a family history (FH+) of SUDs have an 8-fold risk of developing a SUD compared to individuals without a family history (FH-; Merikangas et al., 1998). Multiple factors may contribute to this heightened risk, including family conflict, increased stress, and other inherited traits such as increased impulsivity and higher incidence of externalizing behaviors (V. C. Smith & Wilson, 2016). Neurobiological factors also may exist, particularly related to neural

reward dysfunction. Our literature search yielded eight studies examining reward processing on the MID task in individuals at high familial risk for SUDs.

An initial study examined the influence of parent alcoholism, comparing 13 unaffected children with 13 matched controls, aged 12-16 years (Bjork, Knutson, & Hommer, 2008), who also were free from any other form of psychopathology. Participants completed the MID, and although reward anticipation elicited NAcc activation in all participants, the authors did not see any significant differences between groups of children with or without FH for alcoholism. However, there was a positive correlation between NAcc activation and personality traits like sensation seeking, traits that underlie risk taking behaviors, particularly among adolescents (Byck, Swann, Schalet, Bolland, & Mustanski, 2015). Thus, although family history of SUD did not seem to be directly related to differences in neural reward processing, personality traits that have a high correlation with substance use behaviors were associated with hyperactivation in striatal regions during the anticipation of rewards.

Two additional studies with slightly larger samples than Bjork et al. (2008) did yield significant group differences between offspring with FH+ for alcohol use disorder (AUD) versus offspring with FH- for alcoholism (Andrews et al., 2011; Yau et al., 2012). In one study, Andrews et al. (2011) found that the FH+ group had lower activation in the NAcc, insula, and OFC during reward anticipation, as well as lower NAcc and amygdala activation in response to loss consumption compared to the FH- group. These findings suggest that reward hyposensitivity during both anticipatory and consummatory processing phases may constitute an inherited predisposition to SUDs. Yau et al. (2012) also compared FH+ and FH- for alcoholism groups; however, they added an additional

variable that measured the FH+ group's current alcohol involvement based on description of the frequency and problems associated with how much alcohol the participants currently drank. Thus, they divided their FH+ group into those with "low" versus "high" alcohol involvement. During the reward anticipation phase of the MID, they found that only the FH+ with low current alcohol involvement had significantly lower activation in the NAcc compared to high involvement FH+ and healthy controls (Yau et al., 2012). At first, one may assume that this finding of decreased activation in FH+ participants supports the reward hyposensitivity theory of addiction; however, because this blunted activation was seen only in the low alcohol involvement FH+ group, it actually suggests that reward hyposensitivity may be a resilience factor for SU in individuals who are at genetic risk for developing SUDs. Thus, this latter study may provide support for a reward hypersensitivity model of SUDs.

Three studies from the Michigan Longitudinal Study (MLS; Zucker et al., 2002) also examined offspring of parents with an alcohol use disorder (AUD); however, their sample was aged 18 to mid to late 20s (Martz, Zucker, Schulenberg, & Heitzeg, 2018; Weiland et al., 2013; Weiland, Zucker, Zubieta, & Heitzeg, 2017). The first study compared 49 FH+ with 21 FH- participants during an MID task to examine differences in functional connectivity between groups. Using PPI analyses, they found that the degree of connectivity from the NAcc to the supplementary sensorimotor area (SSMA) and from the NAcc to the right precuneus mediated the relationship between sensation seeking and alcohol consumption in the FH+ group (Weiland et al., 2013). They also found that the FH+ had increased coupling between these regions during reward anticipation (Weiland et al., 2013). These findings may illustrate that among offspring with a genetic risk for

AUD, those with higher personality traits associated with SU (e.g., sensation seeking) exhibit increased communication between regions associated with hedonic value or wanting (e.g., the VS and NAcc) regions important for motor actions (e.g., the SSMA). A second study used data from the MLS (33 FH+ males and 11 FH- controls), and in addition to the fMRI scan visit, participants also completed PET scans in which the MID was completed (Weiland et al., 2017). Further, the authors classified those FH+ participants who had experienced drunkenness by age 15 to be "high risk," as early problematic alcohol use confers greater risk for later problematic SU (Spak, Spak, & Allebeck, 1997). On the fMRI task, no group differences emerged between FH+ low risk, FH+ high risk, and control groups. However, on the MID during PET scanning, being in the FH+ group was associated with increased dopamine release during monetary reward, which supports the reward hypersensitivity theory of SUDs. Finally, Martz et al. (2018) aimed to examine reward processing as a resilience factor in FH+ participants by examining patterns of substance use between ages 17 and 26 post-MRI scanning. They found that higher VS activation during the reward anticipation phase of the MID was positively correlated with frequency of marijuana use and binge drinking between ages 17 and 18 among the FH+ group in general, but that this did not distinguish resilience from risk group (Martz et al., 2018). Thus, they concluded that this could indicate that having a family history of SUD results in similar underlying neurobiology for reward sensitivity, regardless of whether the FH+ individuals develop later SU problems.

Most of the previous studies have very small sample sizes, which greatly limits power for detecting effects. In a much larger study, Muller et al. (2015) compared two groups of 206 adolescent participants each (one with a first or second degree relative with

history of AUD, and the other a control group with no family history of AUD). Additionally, they compared two smaller groups (N=77 each) of participants with at least one biological parent with a history of AUD to those who did not have a biological parent with an AUD. Youth in all groups had relatively low SU and did not differ on key demographic and personality measures. In this study, there were no significant differences between groups in analyses using pre-defined VS regions of interest during reward anticipation and consumption, nor were there any significant results from exploratory whole-brain analyses (Müller et al., 2015).

A final study compared four groups of individuals; one group that had family history significant for SUD and also were stimulant-dependent, one group of their siblings who did not have any SUD, one group who had no familial history of SUD but were non-dependent stimulant users, and a final group who had neither family nor personal history of SUD (Just et al., 2019). This design allowed the authors to examine the interactive effect of familial risk and stimulant drug use on reward processing. Whereas stimulant users exhibited increased activation during reward anticipation in motor areas, familial risk was associated with altered functional connectivity within the corticostriatal regions. Specifically, during reward anticipation, those with familial history of SUD had decreased connectivity between the putamen and ACC, and increased connectivity between the putamen and frontal pole, temporal pole, and brainstem (Just et al., 2019). The authors found no significant brain activation clusters between groups, which suggests that perhaps altered frontostriatal connectivity between regions involved in inhibitory control and reward processing is most important for conferring risk for SUDs.

Contradictory findings within the unaffected offspring literature in SUDs may be explained in the context of the limitations across these studies. First and foremost, most of these studies included very small sample sizes. Second, the age range of participants varied between studies, with some studies examining reward responsivity in early to mid-adolescence (Bjork et al., 2008; Müller et al., 2015), whereas others included young to middle-age adults (Andrews et al., 2011; Yau et al., 2012). Developmental differences in the maturation of the reward circuit across adolescence into adulthood may explain why these studies yielded such different and opposite results (Van Leijenhorst et al., 2010). Additionally, different versions of the MID task were used across studies, and thus, results are not directly comparable because of these methodological differences. Despite mixed findings, there does seem to be some continuity, particularly across functional connectivity analyses, suggesting that an impaired ability to recruit cortico-limbic motivational circuitry is implicated in SUDs.

Neural Reward Dysfunction as a Trait Risk Factor for SUDs

The majority of studies that examine reward function in remitted SUDs take place in clinical settings, and thus, are part of trials aimed at predicting treatment response. Most of these treatment studies find that blunted reward processing in key fronto-striatal regions in response to non-drug related stimuli is associated with worse clinical outcomes (e.g., shorter time to relapse; Moeller & Paulus, 2018). Because interventions themselves may result in neuroplastic changes in the brain, treatment is a confounding variable when examining trait vulnerabilities to SUDs in the reward circuit. Therefore, we excluded any study related to treatment outcomes from our review, and instead, focused on naturalistic studies incorporating remitted SUD groups. However, many of these studies also

included groups of substance users who were in "initial abstinence," which typically refers to the first couple of weeks abstaining from a substance. Thus, initial abstinence does not reflect a state of true remission as defined in the DSM (American Psychiatric Association, 2013), and we excluded these types of studies from our review. We found two studies that used the MID during fMRI to study brain function in groups of individuals in remission from or in prolonged abstinence from substances.

In the first study to compare former and current cocaine users with healthy controls without history of substance use, Patel et al. (2013) found that compared to current cocaine users, former users (in remission for at least 6 months) had less activation to loss anticipation in the frontopolar PFC (defined as BA10). Compared to healthy controls, former cocaine users also had less activation in the right parahippocampal gyrus and right insula during loss anticipation. During loss consumption, former users had increased activation in the right hippocampus compared to controls, and greater activation in the left VTA compared to current users. There were no significant differences between groups during anticipation or consumption of rewards. This study used a relatively large sample of healthy controls (N=153), but there were only 43 and 35 participants in the current and former user group, respectively. Thus, conclusions regarding the robustness of these effects are limited given problems with power. Because former users differed from both healthy controls and current users during different conditions and in different regions, there may be certain reward processes that revert to "baseline" once individuals are in remission, but others that have long-lasting effects on the brain.

A second study examined reward processing on the MID in a sample of current cigarette smokers, former cigarette smokers (in remission for at least one year), and controls (Nestor, McCabe, Jones, Clancy, & Garavan, 2018). Due to the small sample size, the researchers had to collapse across smoking groups in order to yield a significant finding of greater activation in the OFC and anterior insular cortex during loss anticipation and consumption in the collapsed smoker group compared to controls. Additionally, ex-smokers had greater change in activation in the ventral putamen and caudate during loss anticipation compared to current smokers and controls. Together, these findings suggest that in nicotine smokers, neural substrates underlying motivation and incentive salience (i.e. OFC), as well as regions underlying a reward-motor network (i.e. caudate, putamen) may be sensitized to loss avoidance (Nestor et al., 2018).

Conclusions from the remitted SUD literature are difficult to draw given the limitations of these two studies. First, they each examined very different substances of abuse (nicotine vs cocaine) that may act on different regions/receptors and to varying degrees. Additionally, sample sizes differed greatly, and the findings must be interpreted with caution as the analyses were likely underpowered. Nonetheless, it appears that drugs may sensitize a fronto-striatal reward circuit that subserves motivational processes involved in both attaining non-drug rewards and avoiding losses. However, it is important to note that we cannot conclude whether these differences in reward processing in former users reflect features related to pre-existing brain function, exposure to a substance of abuse, or recovery.

Neural Reward Dysfunction as a Pre-existing Risk Factor for SUDs

Cross-sectional research cannot clarify whether aberrant neural responses to rewards precede or result from SU. Thus, to fully understand neural reward function as a pre-existing risk factor for SUDs, longitudinal research is needed to prospectively predict initiation of substance use and onset of SUDs. Our literature search yielded a handful of studies examining neural reward processing in the MID task in adolescents prior to problematic SU. In fact, all these studies used samples in early to mid-adolescence, which is necessary to capture brain function before exposure to drugs. We review the findings from seven eligible studies below.

Four studies used data from the IMAGEN consortium, which is one of the largest studies aimed at increasing our understanding of the neurobiological mechanisms related to behavior and adolescent brain development worldwide (Schumann et al., 2010). As such, there is a large sample of youth in mid-adolescence who have completed fMRI scans and measures of SU at multiple time points. Of note, the MID task in the IMAGEN study only featured reward anticipation and outcome phases. An initial investigation by Whelan et al. (2014) aimed to discover what factors predicted current and future alcohol use, using machine learning in a sample of over 600 youth. The authors classified future binge drinkers as those participants who only had 3-5 lifetime drinks (but no binge drinking episodes) by age 14, but had at least three binge drinking episodes by age 16 (Whelan et al., 2014). They found that future binge drinkers had reduced activation in occipito-temporal and posterior cingulate regions to reward anticipation, and reduced activation in the left temporal pole and increased activation in the bilateral superior frontal gyrus to reward consumption at age 14. Baker et al. (2019) extended the previous

findings by examining interactions between the VS and OFC. Although they found that no ROIs uniquely predicted alcohol use, significant interactions between the medial OFC and the VS, as well as between the lateral OFC and VS, during anticipation of high rewards were associated with current alcohol use at age 14. However, these interactions were not significant predictors of future alcohol use at age 16. These findings suggest that the degree of connectivity between OFC and VS regions may be a correlate of current early alcohol use, but does not predict future alcohol use in adolescence. Whereas Whelan et al. (2014) found blunted activation to reward anticipation and blunted and heightened activation to reward consumption predicted future alcohol use, Baker et al. (2019) found no prospective predictions.

A recent study by Büchel and colleagues (2017) examined brain function in adolescents who were characterized as being high novelty seekers via personality questionnaire at age 14, and whether it could predict who would develop problematic SU at age 16. They found that those participants who went on to develop problematic drug use had decreased right VS, left midbrain, and right dlPFC activation to large reward anticipation at age 14. These findings suggest that among high novelty seeking adolescents, reward hyposensitivity underlies risk for developing problematic SU later in adolescence. However, although there were no diagnosable SUDs among participants, the sample was not completely naïve of all substances at baseline. Heinrich et al. (2016) utilized IMAGEN data to examine what factors were most important in explaining increased alcohol use across adolescence. In their four-factor model, they found that personality traits and genetic factors contributed more than reward-related brain function to the prediction of alcohol use (Heinrich et al., 2016). Thus, even though there are

differing brain reward profiles that may differentiate and predict problematic alcohol use, it appears that other factors such as personality traits may be more important in conferring risk for SU.

Indeed, genetic factors may play an important role in reward circuit sensitivity in general. In one study using data from the Michigan Longitudinal study (described above), the authors attempted to examine reward processing as well as genetic factors and their association with alcohol use across time in 175 adolescents (Heitzeg et al., 2014). Participants had anywhere between one and four scans in which they completed an MID. In addition, most of the sample was at high risk due to having a parent with an AUD. They found that heightened NAcc activation to reward anticipation trials was associated with alcohol use across adolescence. Additionally, variations in the GABRA2 gene (which is known to be associated with alcoholism in adulthood as well as with impulsivity and externalizing behaviors) were associated with differences in NAcc activation (Heitzeg et al., 2014). Specifically, NAcc activation to reward anticipation mediated the relationship between genotype and future problematic alcohol use, suggesting an interplay between genes, reward-related brain function, and future SU.

Another study examined 73 youth (average age 14) during a card-guessing paradigm, and categorized the youth into two groups: those who were substance users (defined as drinking more than a few sips of alcohol or any illicit drug use) and those who were not, about 24 months after scanning (Bertocci et al., 2017). Thirty-six reported SU post-scan. The authors found that increased activation in the left middle PFC to reward consumption and decreased left ventral anterior insula activation to loss consumption predicted membership in the substance user group at 24 months. When

removing 15 youth who had SU at the time of scan, only increased left middle PFC activation to reward consumption predicted SU, which suggests that left ventral anterior insula activity to loss may be driven by prior SU. One major limitation of this study was that the substance analyses were post-hoc, and thus, the authors could not control for SU at time of scanning. Additionally, some participants were taking psychotropic medication.

Finally, and the methodologically strongest study of future SU, Cope et al. (2019) examined brain activation in 34 participants aged 8 to 12 at time of scan. Their sample was at high risk because the majority (82%) had a FH+ for AUD. In order to be eligible for this study, participants could not have had any SU prior to scanning. Beta coefficients from ROIs indicated that the only significant predictor of SU initiation at age 16 was higher NAcc activation during anticipation of large rewards. This supports the reward hypersensitivity theory of SUDs. Despite this study's strength in that no participants had tried substances prior to scanning, the sample also had other diagnoses (e.g., ADHD, depression, externalizing disorders), which is characteristic of children at high familial risk for SUDs. Additionally, the sample size was small, and thus, the results should be interpreted within the confines of low power.

Even among prospective findings, there are still conflicting results about whether problematic SU is driven by reward hypo- or hypersensitivity. However, these studies suggest that differences in activations in both striatal and cortical regions, aberrant functioning in the mesolimbic reward motivation system, as well as impaired prefrontal control may confer risk for future SU. Even though methodologically strong, these longitudinal studies also have their limitations. For example, given the young samples,

the majority of studies measured "problematic" SU through questionnaires, and not by actual DSM criteria for SUDs. Thus, there is a question of how pathological this initiation of problematic SU is in adolescence, as most participants did not reach clinical threshold (Cope et al., 2019). Moreover, most of the substances used by adolescents were legal drugs (e.g., nicotine, marijuana, alcohol), and thus, may not capture the severity of those who engage in illicit drug use (Büchel et al., 2017). These types of prospective studies need to be extended into later adolescence and adulthood to ascertain the extent to which these findings contribute to the development of actual SUDs. Additionally, only one study (Cope et al., 2019) used a completely substance naïve sample at baseline, and even this study had a small sample size. Thus, longitudinal studies need to be refined to target adolescents prior to any substance initiation. They also need to be extended for longer periods of time to capture developmental effects of reward processing from initiation of SU in adolescence through to the development of pathological SUDs in adulthood.

Summary of Findings from Neuroimaging Literature of SUDs

An interesting pattern that emerged in the SUDs literature is that a substantial number of studies did not find significant differences in activation across family history, remitted, and prospective studies. Of the studies that did yield significant results, the majority of them focused on the reward and anticipation phases. It appears that the literature on high familial risk and remitted SUDs is mixed, with some reporting hypo- and some reporting hyper-activations particularly in striatal regions. Unfortunately, the prospective literature does not clarify these mixed findings much. Although the majority of the studies report blunted activations in striatal and frontal regions during reward processing, a couple of methodologically strong studies (e.g., with samples who never

took any substances) suggest that heighted NAcc activation, particularly during reward anticipation, may underlie a vulnerability to initiate SU. Furthermore, some suggest that reward function may not be as important for the development of SU, and that genetics and personality traits drive this vulnerability for SU (Heinrich et al., 2016; Heitzeg et al., 2014). What is lacking in the SUDs literature are analyses related to fronto-striatal connectivity; thus, future research should focus on the extent to which communication within the reward circuit predicts SUDs.

Summary and Integration

Results from this literature review yielded a limited number of studies that examined reward processing on the fMRI MID or card-guessing tasks in individuals at risk for developing BSDs or SUDs. Furthermore, the results were mixed, making it difficult to draw conclusions regarding whether reward circuit hypo- or hypersensitivity is a risk factor for both BSDs and SUDs. Additionally, given the variety of study designs included in this review, it is difficult to compare results across the extant literature. We elaborate on the reasons for these discrepancies, address important limitations, and provide suggestions for future directions and improved methodology.

First, during adolescence, the fronto-striatal reward circuit goes through rapid and drastic changes, maturing relatively quickly and prior to other prefrontal regions associated with the cognitive control network (McClure et al., 2004). This maturational imbalance between the reward and cognitive control networks is hypothesized to be a reason why adolescence is a period of increased risk for engaging in risky behaviors such as SU (Steinberg, 2010). Thus, even normative reward processing during adolescence differs from reward processing during adulthood; consequently, from a developmental

perspective, one cannot directly compare brain processes between these age epochs. Additionally, most of the research conducted has been cross-sectional, and thus, does not capture any of these developmental nuances. In order to capture changes in brain development and their contributions to the development of SUDs and BSDs, it is important to conduct larger, longitudinal studies utilizing within person designs to assess trajectories throughout adolescence into adulthood.

Second, the effects of prior treatment with psychotropic medication and prior SU confounds studies that aim to identify pre-existing neural markers, because these substances change brain structure and function. To resolve this issue, some researchers included only people who were never treated (e.g., Yip et al., 2015) or who never initiated SU (e.g., Cope et al., 2019). However, in so doing, these studies also restricted the variance of disorder severity in their samples. For example, individuals who do not require intervention have less severe forms of BSDs (e.g., BDNOS), and thus, may not be directly comparable to those with more severe forms. Indeed, a similar issue exists for studies examining the onset of SUDs in that they recruit very young children, who never meet clinically significant cut-offs for DSM disorders. Furthermore, in examining such young children, one is unable to draw conclusions regarding normative risk-taking versus more problematic SU that may develop later in adolescence or in adulthood. Thus, this raises the question of whether these studies are capturing brain dysfunction in the reward circuit that is clinically relevant. Again, to resolve this issue, larger longitudinal studies are needed to follow groups of participants for extensive periods of time, from late childhood/early adolescence into adulthood.

Third, except for the small number of studies that actively sought to exclude participants with comorbidities, most of the studies included participants who had more than one psychiatric diagnosis. In including people with multiple diagnoses, it is not possible to draw conclusions about what mechanisms are unique to a single disorder; however, this approach is more reflective of the actual BSD and SUD populations. Perhaps such samples are most relevant translationally as comorbidity accurately reflects patient populations and the high incidence of different diagnoses among people with BSDs and SUDs. It also may be prudent to move away from approaches in which one compares distinct groups of participants to approaches that are more in line with an RDoC perspective, which considers how brain-behavior relationships and mechanisms influence specific symptoms. Using an RDoC approach in identifying common domains may be a better way to operationalize the high co-occurrence of BSDs and SUDs.

A final important limitation across the reviewed studies relates to studying reward processing with the MID or card-guessing tasks. First, researchers differed in the version of the tasks that they used. Some utilized a card-guessing paradigm that included a "decision-making" component, whereas others required only a button press to a target. Whether an active response to attain rewards and/or avoid losses is required or not in the task has an important impact on which regions of the neural reward circuitry are likely to be activated and involved in functional connectivity patterns (Haber & Knutson, 2010). Whereas some tasks displayed actual dollar amounts of rewards and losses, others used tokens representative of a monetary reward. Furthermore, different studies used different magnitudes of money (e.g., $1 versus $5). Thus, the heterogeneity across monetary reward tasks may confound findings. Additionally, different task durations may impact

neural responses because activation in certain regions, particularly the OFC, only may occur after lengthy anticipation phases (Diekhof, Kaps, et al., 2012). There also may be individual differences in salience and motivation for monetary rewards during reward processing. Even though meta-analyses demonstrate the validity of a number of different monetary reward tasks in activating neural reward regions, the above limitations still should be taken into consideration (Oldham et al., 2018).

Proposed Theoretical Integration

In line with the newer RDoC perspective, it is important to identify common mechanisms of vulnerability across psychiatric disorders, and this approach may be particularly useful in understanding the high co-occurrence of BSDs and SUDs. Indeed, one key theory of why BSDs and SUDs have such high co-occurrence suggests that it is a result of their shared common mechanisms related to modulating motivation and reward responsivity (Swann, 2010). It is abundantly clear that both disorders are characterized by dysfunction in the neural reward circuit; however, the direction and precise nature of these abnormalities remains unclear given the discrepancies in the extant literature. As discussed previously, definitive conclusions cannot be drawn without addressing numerous limitations in the literature. Nonetheless, we argue for and expand on the multifinality/equifinality perspective described by Nusslock and Alloy (2017), where multifinality suggests that the same mechanisms can result in different outcomes (e.g., BSDs and SUDs), and equifinality suggests that the same outcome (e.g., SUD) can result from different mechanisms (Whitton, Treadway, & Pizzagalli, 2015). In their review of reward processing in a number of psychiatric disorders, Nusslock and Alloy (2017) conclude that considering reward function profiles across disorders is best done using a

equifinality/ multifinality perspective. Thus, we propose that it is possible that both hypo- and hyper-sensitivity in the reward circuit may contribute to the development of BSDs and SUDs via different mechanisms.

For example, individuals with a blunted reward system may engage in SU to attenuate dysphoria and increase their positive affect. In other words, they seek exogenously (in substances of abuse), what they lack endogenously. This same blunted reward profile may underlie a vulnerability to develop BSDs as well. For example, some researchers found that reduced activation in the striatum (both dorsal and ventral), as well as blunted activation in regions associated with affect regulation, was observed in at-risk individuals (children with familial history of BSD), and in euthymic individuals with BSDs (Schreiter et al., 2016; Singh et al., 2014; Yip et al., 2015). Thus, this is an example of the multifinality perspective -- reward hyposensitivity may lead to both BSDs and SUDs. On the other hand, initiation of SU (and over time SUDs) may be driven by reward hypersensitivity, instantiated in strong approach behavior toward rewards (including substances of abuse), as also evidenced by the current literature review (Cope et al., 2019). Again, this demonstrates the multifinality perspective, in that reward hypersensitivity may underlie two separate disorders. The reward processing abnormalities that contribute to the development of BSDs and SUDs also can reflect equifinality processes because both reward hypo- and hyper-sensitivity may explain initial vulnerability to these disorders depending on the target of these different pathways (e.g., increased sensation-seeking via hypersensitivity versus attenuating dysphoria via hyposensitivity). Expanding on Nusslock and Alloy's perspective, we argue that reward

hypo- and hyper-sensitivity may underlie a propensity to initially develop both BSDs and SUDs.

To further expand on this perspective, we propose that whether reward processing dysfunction in the initial onset of BSDs and SUDs is due to equifinality or multifinality processes relies on additional factors. It is clear from the current review that genes are important in determining reward processing in people at risk for SUDs and BSDs, because certain genotypes may play a role in influencing reward circuit function itself. For example, Heitzeg et al. (2014) found that a particular variation in a gene known to be associated with adult AUD was associated with different levels of striatal activation during reward processing. Additionally, researchers have found genome-wide associations for both BSDs and SUDs, and many of these common genes are crucial in the initial development of brain function, which suggests that there is an interplay between genes, brain function, and onset of BSDs and SUDs (Johnson, Carver, Mulé, & Joormann, 2013). It is possible that the expression of different genes may result in varying degrees of reward sensitivity within the fronto-striatal circuit. One future direction would be to identify what genes play a role in reward circuitry development and whether they are equally associated with BSDs and SUDs. Identifying these different gene variants may prove to be an important platform to study the interaction between brain function and the development of these disorders, specifically because Heinrich et al. (2016) suggests that genetic factors account for a greater degree of variance in SUD outcomes than does brain function.

Finally, we propose that equifinality and multifinality perspectives on reward processing dysfunction also must be considered in the context of functional connectivity

within the reward circuit, as well as between the reward circuit and other regions responsible for cognitive control. In other words, it is important to understand that abnormal striatal reward responses may not only be influenced by genetic variations, but also by differences in bottom-up/top-down neural responses to rewards. For example, aberrant responding in the reward circuit may be driven by a disproportionate bottom-up response from the striatum, or via dysfunctional top-down control by prefrontal areas. Indeed, our review suggests that aberrant fronto-striatal connectivity during reward processing may underlie a vulnerability to developing poor regulation and modulation over behaviors related to motivation and pursuit of goals. Reward processing is not a unitary construct, and the same disorder may result from different reward system abnormalities, while dissimilar symptoms may arise from common mechanisms. Although the goal of this review was to understand the shared neural reward processing mechanisms in BSDs and SUDs, it is important to note that this is just one piece of a very complex puzzle.

Conclusion

In the current review, we identified an array of studies from the BSD and SUD literatures in an attempt to understand the neural substrates underlying vulnerability to developing BSDs and SUDs with an aim to shed light on potentially common mechanisms responsible for their high co-occurrence. We propose that aberrant responding and connectivity across neural regions associated with reward and cognitive control confers risk for the development of BSDs and SUDs; however given the heterogeneity in study designs and samples, we cannot definitively state the exact nature of this dysfunction. Instead, we propose an equifinality/multifinality perspective in that

similar neural reward processing dysfunctions can lead to both BSDs and SUDs and different neural reward processing abnormalities can lead to a single outcome (e.g., SUDs). Future directions should focus on more definitively determining the reward processing profiles involved in risk for BSDs and SUDs, and how this influences the course of both disorders.

Table 16. Studies included in the systematic review (Bipolar Spectrum Disorders).

Reference	Sample Description	Age, Mean (SD)	Female, No. (%)	fMRI task/ Analysis Type	Main Results
Offspring Studies					
Singh et al. (2014)	20 offspring of BP1 parents (high risk) and 25 offspring of parents (and had first and second degree relatives) without psychopathology (low risk)	BSD offspring: 12.7 (2.9) Control offspring: 11.8 (2.4)	High Risk: 13 (65%) Low Risk: 15 (60%)	MID/ Voxelwise; Connectivity (PPI)	• BSD offspring had less pregenual cingulate activation during loss anticipation compared to reward anticipation, and compared to control offspring • BSD offspring had greater left lateral OFC activation during reward feedback compared to avoided losses feedback, and compared to control offspring • BSD offspring had greater connectivity between the pregenual cingulate and right vlPFC during reward anticipation compared to loss anticipation. • BSD offspring had greater connectivity during loss anticipation and less connectivity during reward anticipation between the pregenual cingulate and right vlPFC compared to control offspring • No significant group differences for reward consumption
Manelis et al. (2016)	29 offspring of BP1, BPII, or BPNOS parents, 28 offspring of parents with non-BSD psychopathology, 23 offspring of parents with no psychopathology	BSD offspring: 13.8 (2.5) nBSD offspring: 13.9 (2.4) Control offspring: 13.7(1.8)	BSD offspring: 6(21%) nBSD offspring: 7(25%) Control offspring: 11(48%)	Card-guessing task/ ROI; Connectivity (PPI)	• BSD offspring had greater activation in the right frontal pole across trials than control offspring • BSD offspring had greater connectivity between VS and right vlPFC during non-reward vs. reward trials than nBSD offspring and control offspring.

Table 16. (continued)

Reference	Sample Description	Age, Mean (SD)	Female, No. (%)	fMRI task/ Analysis Type	Main Results
Soehner et al. (2016)	25 offspring of BPI or BPII parents and 21 offspring of parents with no psychopathology	BSD offspring: 14.20(2.3) Control offspring: 14.0(2.2)	BSD offspring: 11(44%) Control offspring: 11 (52%)	Card-guessing task/ ROI; Connectivity (PPI); Whole brain	• BSD offspring had less activation in right posterior insula during reward trials compared to control offspring. • BSD offspring had greater connectivity between the VS and left posterior insula during reward trials than control offspring • Similar findings in whole-brain analyses
Acuff et al. (2019)	32 offspring of BSD parents, 36 offspring of parents with non-BSD psychopathology, and 29 offspring of parents with no psychopathology	BSD offspring: 14.0(2.4) nBSD offspring: 14.1(2.3) Control offspring: 13.9(1.8)	BSD offspring: 16(50%) nBSD offspring: 14(39%) Control offspring: 18(46%)	Card-guessing task/ ROI; Connectivity (PPI)	• BSD offspring had lower connectivity between the VS and left cACC during loss trials compared to nBSD and control offspring. • BSD offspring had greater connectivity between the pars orbitalis and OFC during reward trials compared to nBSD offspring • nBSD offspring had lower connectivity between pars orbitalis and right OFC during reward trials compared to control offspring • BSD offspring had greater connectivity between the pars triangularis and right OFC during loss trials compared to control offspring

Table 16. (continued)

Reference	Sample Description	Age, Mean (SD)	Female, No. (%)	fMRI Task/ Analysis Type	Main Results
Euthymic Studies					
Nusslock et al. (2012)	21 euthymic BPI and 20 healthy controls	Euthymic: 31.5(8.7) Controls: 31.6(6.9)	Euthymic: 12(57%) Controls: 12(60%)	Card-guessing task/ ROI; Whole brain	• Euthymic BSD had greater right VS activation during reward anticipation compared to controls, and greater bilateral VS activation during reward anticipation compared to loss anticipation • Euthymic BSD had greater right OFC activation during reward anticipation compared to controls and compared to loss anticipation • Euthymic BSD had greater left-lateral OFC activation during reward anticipation compared to controls • No significant group differences during loss anticipation or during consumption phases
Caseras et al. (2013)	32 euthymic BPI (N=17) or BPII (N=15) and 20 healthy controls	Euthymic BPI: 42.8(7.3) Euthymic BPII: 40.5(8.1) Controls: 42.3(6.0)	Euthymic BPI: 11(64%) Euthymic BPII: 9(60%) Controls: 13(65%)	Card-guessing task/ ROI; Whole brain	• Euthymic BPII had greater bilateral VS activation during reward anticipation compared to controls and euthymic BPI. • Euthymic BPI had greater right VS activation during reward outcome compared to euthymic BPII • Euthymic BPII had greater activation in the left vlPFC, insula, precentral gyrus, and middle and superior temporal cortex during reward anticipation compared to controls and euthymic BPI

Table 16. (continued)

Reference	Sample Description	Age, Mean (SD)	Female, No. (%)	fMRI Task/ Analysis Type	Main Results
Caseras et al. (2013) cont'd					• Euthymic BPII had greater activation in the bilateral caudate nuclei and left dlPFC during reward anticipation compared to healthy controls • No significant group differences for reward outcome in whole brain-analyses
Yip et al. (2015)	20 euthymic BPII or BPNOS and 20 healthy controls	Euthymic: 22.6(0.9) Controls: 22.1(.6)	Euthymic: 8(40%) Controls: 10(50%)	MID/ ROI; Whole brain	• Euthymic BSD had lower activation in the right DS during reward anticipation compared to controls. • Euthymic BSD had lower activation in the right VS and right DS during loss anticipation compared to controls • No significant group differences for any other MID phase in VS and DS.
Schreiter et al. (2016)	20 euthymic BPI or BPII and 20 healthy controls	Euthymic: 41.6(10.1) Controls: 41.5(7.3)	Euthymic: 12(60%) Controls: 12(60%)	MID/ ROI; Connectivity (PPI)	• Euthymic BSD had lower activation in the left and right VS during reward anticipation (but not loss anticipation) compared to controls • Euthymic BSD had weaker connectivity between the left VS and aPFC during reward anticipation compared to controls
Dutra et al. (2015)	24 euthymic BPI and 25 healthy controls	Euthymic: 31.4(11.9) Controls: 29.4(8.8)	Euthymic: 15(63%) Control: 15(60%)	MID and SID/ ROI; Whole brain	• Euthymic BSD had lower activation in the OFC, bilateral interior frontal gyri, and right lateral occipital cortex during monetary and social reward anticipation compared to controls • Euthymic BSD had greater activation in the NAcc during monetary and social reward consumption compared to controls

Table 16. (continued)

Reference	Sample Description	Age, Mean (SD)	Female, No. (%)	fMRI Task/ Analysis Type	Main Results
Dutra et al. (2015) cont'd					• Euthymic BSD had greater activation in the right NAcc, right caudate and bilateral thalamus during reward consumption compared to controls
Dutra et al. (2017)	24 euthymic BPI and 25 healthy controls	Euthymic: 31.4(11.9) Controls: 29.4(8.8)	Euthymic: 15(63%) Control: 15(60%)	MID and SID; Connectivity (whole brain seed-based)	• Euthymic BSD had stronger connectivity between left VS and left OFC during monetary and social reward consumption compared to controls • Euthymic BSD had weaker connectivity between the right VS and mPFC during omission of expected monetary and social reward compared to controls • Euthymic BSD had stronger connectivity between the bilateral VS and left amygdala during monetary and social reward consumption compared to controls
Kollman et al. (2017)	Sample 1: 16 euthymic BPI and 24 healthy controls	Euthymic: 43.3(11.3) Controls: 42.7(10.2)	Euthymic: 10(63%) Controls: 12(50%)	MID; ROI	• Euthymic BSD had greater activation in the ACC (but not VS, OFC, or insula) during reward anticipation compared to controls

Note. BSD offspring did not have a BSD diagnosis; BPI = Bipolar Disorder, type I; BPII = Bipolar disorder, type II; BSD = Bipolar Spectrum Disorder; MID = Monetary Incentive Delay; SID = Social Incentive Delay; ROI = regions-of-interest; PPI = psychophysiological interaction; VS = ventral striatum; OFC = orbitofrontal cortex; vlPFC = ventrolateral prefrontal cortex; (c)ACC = (central) anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; DS = dorsal striatum; aPFC = anterior prefrontal cortex; NAcc = nucleus accumbens; mPFC = medial prefrontal cortex

Table 17. Studies included in the systematic review (Substance Use Disorders)

Reference	Sample Description	Age, Mean (SD)	Female, No. (%)	fMRI task/ Analysis Type	Main Results
Familial Risk Studies					
Bjork et al. (2008)	13 offspring of at least one parent with alcoholism (FH+) and 13 offspring of parents without alcoholism (FH-)	FH+ offspring: 13.9(0.4) FH- offspring: 13.8(0.4)	FH+ offspring: 5(38%) FH- offspring: 5(38%)	MID/ VOI	• FH- offspring had lower activation in the right anterior insula during loss consumption compared to FH+ offspring. • No group differences in activation in VS during reward anticipation, or in mesofrontal cortex and VS during reward consumption
Andrews et al. (2011)	19 offspring of father with alcohol dependence and one first or second degree relative with alcohol dependence/abuse (FH+) and 30 offspring with no first or second degree relatives with alcohol abuse/dependence (FH-)	FH+ offspring: 33.7(13.6) FH- offspring: 33.6(14.4)	FH+ offspring: 13(69%) FH- offspring: 19(63%)	MID/ ROI	• FH+ offspring had lower activation in the NAcc, insula and OFC during reward anticipation compared to FH- offspring • FH+ offspring had lower activation in the amygdala and NAcc during loss consumption compared to FH- offspring • No group differences for reward consumption

Table 17. (continued)

Reference	Sample Description	Age, Mean (SD)	Female, No. (%)	fMRI Task/ Analysis Type	Main Results
Yau et al. (2012)	20 offspring of at least one parent with AUD (FH+) and 20 offspring with no parental AUD history (FH-)	FH+ offspring: 20.2(1.2) FH- offspring: 20.1(1.3)	FH+ offspring: 8(40%) FH- offspring: 8(40%)	MID/ ROI; Whole brain	• FH+ offspring had lower activation in the right NAcc during reward anticipation and in the NAcc during loss anticipation compared to FH- offspring • FH+ offspring who were also low-risk drinkers had lower activation in the NAcc during reward and loss anticipation compared to high-risk FH+ offspring and FH- offspring
Weiland et al. (2013)	49 offspring of at least one parent with AUD (FH+) and 21 offspring with no parental AUD history (FH-)	FH+ offspring: 20.1(1.3) FH- offspring: 20.1(1.3)	FH+ offspring: 32(65%) FH- offspring 14(67%)	MID/ ROI; Connectivity (PPI)	• FH+ offspring had stronger connectivity between the NAcc and the SSMA, precuneus, paracentral lobule, and sensorimotor areas during reward anticipation compared to FH- offspring (who exhibited weaker connectivity between these areas)
Muller et al. (2015)	206 children with first or second degree relative with AUD (FH+) and 206 children with no biological relative with AUD (FH-)	FH+ group: 14.6(0.4) FH- group: 14.6(0.4)	FH+ group: 100(49%) FH- group: 100(49%)	MID; ROI Whole brain	• No significant group differences during reward anticipation or feedback, even when including only subjects who had a biological parent with AUD.

Table 17. (continued)

Reference	Sample Description	Age, Mean (SD)	Female, No. (%)	fMRI Task/ Analysis Type	Main Results
Weiland et al. (2017)	9 offspring of at least one parent with AUD who initiated drinking prior to age 15 (high risk FH+), 24 offspring of at least one parent with AUD who did not initiate drinking prior to age 15 (low risk FH+) and 11 offspring with no first or second degree relatives with AUD (FH-)	High risk FH+: 24.2(2.9) Low risk FH+: 22.0(2.8) FH-: 20.6(2.7)	N/A – Sample was all male	MID; ROI	• No significant group differences in the NAcc during reward anticipation or feedback
Martz et al. (2018)	57 offspring of at least one biological parent with SUD (FH+) further divided into a resilient group (N = 21; no binge drinking/marijuana use) or high risk group (N = 36; presence of binge drinking/marijuana use)	High risk FH+: 20.5(1.2) Resilient FH+: 20.8(1.5)	High risk FH+: 9(25%) Resilient FH+: 7(33%)	MID; Whole brain	• No significant group differences during reward anticipation

Table 17. (continued)

Reference	Sample Description	Age, Mean (SD)	Female, No. (%)	fMRI Task/ Data Analysis	Main Results
Just et al. (2019)	41 offspring of at least one biological parent with SUD and were themselves stimulant dependent (F+S+) along with their non-stimulant dependent siblings (F+S-), 25 non-dependent stimulant users without familial history of SUD (F-S+) and 48 controls without family history or personal history of addiction (F-S-)	F+S+: 34.6(7.4) F+S-: 32.3(8.4) F-S+: 28.6(6.6) F-S-: 32.5(8.8)	F+S+: 4(10%) F+S-: 24(54%) F-S+: 12(48%) F-S-: 18(38%)	MID; Whole brain Connectivity (PPI)	• FH+ offspring had greater activation in the left occipital pole during reward anticipation compared to FH- offspring. • FH+ offspring had stronger connectivity between the putamen and the frontal pole, temporal pole, and brainstem, as well as weaker connectivity between the putamen and ACC during reward anticipation compared to FH- offspring. • F-S+ and F+S- offspring had stronger connectivity between the putamen and bilateral precentral gyrus, bilateral lateral occipital cortex and right postcentral gyrus during reward anticipation compared to F+S+ and F-S- offspring, respectively.
Remitted Studies					
Patel et al. (2013)	42 current cocaine users, 35 former cocaine users, and 47 healthy controls	Current users: 38.5(7.1) Former users: 38.5(7.6)	Current users: 18(42%) Former users: 9(26%)	MID; ROI	• Former users had lower activation in the frontopolar PFC during loss anticipation compared to current users. • Former users had lower activation in the right parahippocampal gyrus and right insula during loss anticipation compared to controls • Former users had greater activation in the right hippocampus during loss consumption compared to

Table 17. (continued)

Reference	Sample Description	Age, Mean (SD)	Female, No. (%)	fMRI Task/ Data Analysis	Main Results
Patel et al. (2013) cont'd		Controls: 34.6(9.0)	Controls: 21(45%)		control, and great activation the left VTA during loss consumption compared to current users. • No group differences during reward anticipation or consumption
Nestor et al. (2018)	15 current cigarette smokers, 10 ex-smokers, and 15 controls	Smokers: 23.3(1.2) Ex-smokers: 25.4(1.6) Controls: 23.8(1.2)	Smokers: 9(60%) Ex-smokers: 7(70%) Controls: 7(47%)	MID; Whole brain	• Both smokers and ex-smokers had greater activation in the OFC and anterior insular cortex during loss anticipation and consumption compared to controls • Ex-smokers had greater activation change in the ventral putamen during loss anticipation compared to smokers and controls, and greater activation change in the caudate during loss anticipation compared to controls.
Prospective Studies					
Heitzeg et al. (2014)	76 children/early adolescents and 99 late adolescents/young adults	Early adolescents: 10.8(1.2) Late adolescents: 20.3(1.4)	Not reported separately per group	MID; VOI	• Greater activation in the NAcc during reward anticipation was associated with increased alcohol use across multiple timepoints through adolescence.

Table 17. (continued)

Reference	Sample Description	Age, Mean (SD)	Female, No. (%)	fMRI Task/ Data Analysis	Main Results
Whelan et al. (2014)	121 future binge drinkers and 115 current binge drinkers	Future: 14.5(.4) Current: 14.6(.4)	Future: 52(43%) Current: 65(57%)	MID; Voxel-wise	• Lower activation in the occipto-temporal and posterior cingulate regions during reward anticipation, and lower activation in the left temporal pole and greater activation in the bilateral superior frontal gyrus during reward consumption at age 14, predicted binge drinking at age 16
Bertocci et al. (2016)	73 youth	13.9(2.0)	30(41%)	Card-guessing task; ROI	• Greater activation in the left middle PFC to reward consumption and decreased activation in the left ventral anterior insula during loss consumption predicted substance use 24 months post-scan.
Heinrich et al. (2016)	736 youth	14.4(0.4)	389(53%)	MID; ROI	• Four-factor model suggests that personality traits and genetic factors contributed more than reward-related brain function to the prediction of future alcohol use
Büchel et al. (2017)	72 novelty seeking youth who developed problematic drug use (PDU) and 72 controls	PDU: 14.4(0.5) Controls: 14.5(0.4)	PDU: 41(57%) Controls: 45(63%)	MID; VOI Whole brain	• Lower activation in the right VS, left midbrain and right dlPFC during anticipation of large rewards at age 14 predicted problematic substance use at age 16
Baker et al. (2019)	1639 youth	14.6(0.4)	847(52%)	MID; ROI	• Interactions between the medial OFC and VS, and between the lateral OFC and VS during anticipation of high rewards was associated with current alcohol use at 14, but was not predictive of alcohol use at age 16

Table 17. (continued)

Reference	Sample Description	Age, Mean (SD)	Female, No (%)	fMRI Task/ Data Analysis	Main Results
Cope et al. (2019)	34 substance-naïve youth	10.5(1.2)	9(26%)	MID; ROI	• Greater activation in the NAcc during reward anticipation (but not loss anticipation) predicted initiation of substance use

Note. FH+/- = family history positive/negative; MID = Monetary Incentive Delay; VOI = volume-of-interest; VS = ventral striatum; ROI = Region-of-interest; NAcc = nucleus accumbens; OFC = orbitofrontal cortex; AUD = alcohol use disorder; SUD = substance use disorder; SSMA = somatosensory motor area; PFC = prefrontal cortex; VTA = ventral tegmental area; PPI = psychophysiological interaction; dlPFC = dorsolateral prefrontal cortex

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