

**A Longitudinal Study of Reward Functioning and Symptom Fluctuation in Mood
Disorders**

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THESIS

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
AMW	Amount of money won
BAI	Beck Anxiety Inventory
BAS	Behavioral Activation System
BAS-RR	Behavioral Activation Scale-Reward Responsiveness
BDI	Beck Depression Inventory II
BIS/BAS	Behavioral Inhibition System/Behavioral Activation System Scale
BOLD	Blood oxygen level dependent
BP	Bipolar disorder
dACC	Dorsal anterior cingulate cortex
DMN	Default mode network
DSM-5	Diagnostic and Statistical Manual 5
eBP	Euthymic bipolar disorder
fMRI	Functional magnetic resonance imaging
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
HC	Healthy control
HMD	History of mood disturbance
ICC	Intraclass correlation coefficient
MDD	Major depressive disorder
MIDT	Monetary Incentive Delay Task
MNI	Montreal Neurological Institute
MPFC	Medial prefrontal cortex
NAcc	Nucleus accumbens
NOS	Not otherwise specified
OFC	Orbitofrontal cortex
PANAS	Positive and Negative Affect Scale
PCC	Posterior cingulate cortex
PFC	Prefrontal cortex
RDoC	Research Domain Criteria
rMDD	Remitted MDD
ROI	Region of interest
rsFC	Resting-state functional connectivity
SEN	Salience and emotion network
SHAPS	Snaith Hamilton Pleasure Scale
SPM8	Statistical Parametric Mapping Version 8
TEPS	Temporal Experience of Pleasure Scale
VLPFC	Ventral lateral prefrontal cortex
VS, VS _i , VS _s	Ventral striatum, inferior and superior
VTA	Ventral tegmental area
W-N	Win minus neutral
YMRS	Young Mania Rating Scale

SUMMARY

Mood disorders represent a major public health and economic burden in the United States. Major depressive disorder (MDD) and bipolar disorder (BP) are chronic, debilitating diseases and existing strategies for relapse prediction and prevention could be improved. A clearer understanding of reward functioning, which is highly disrupted in active phases of MDD and BP, during the euthymic phase of illness may improve our model of how these disorders manifest and recur. Reward functioning deficits are documented extensively in the literature, but few studies have evaluated and directly compared self-report, task, and neural facets of reward functioning in a combined sample of remitted MDD and euthymic BP individuals over time. We hypothesized that, individuals with a history of mood disorders (HMD) would have lower trait positive affect, worse performance on reward processing tasks, increased connectivity from key regions in the reward circuit to the salience and emotion network (SEN) and default mode network (DMN), and more homogeneity in the SEN and DMN. We expected baseline self-reported reward responsiveness to predict fluctuations in mood symptoms over time in the HMD group and moderate the effect of diagnosis on mood symptoms over time. We explored whether reward task performance predicted depressive symptom change in a cross-lagged manner over time in the HMD group. Participants were 132 individuals with HMD and 42 healthy controls (HC). After undergoing symptom and diagnostic assessment by a clinician, participants completed resting-state and task-based fMRI, a neuropsychological battery including a reward task, and self-report measures of symptoms, reward and affective functioning. A subset of participants completed two additional study visits over a follow-up period of approximately three years, repeating the clinician assessments, self-report measures, and behavioral tasks. Self-reported affect and reward functioning differentiated the HMD and HC groups, whereas

objective measurements of reward failed to differentiate groups or to predict naturalistic symptom fluctuation. Resting-state connectivity differences emerged that suggested increased connectivity between reward nodes and salience regions and decreased connectivity between reward nodes and default mode regions in HMD participants. Homogeneity, as assessed by variance between reward seeds and the SEN and DMN, did not differ between groups. Our hypotheses regarding moderators and mediators were not supported. Overall, rsFC may be more sensitive to trait biomarkers of disease, relative to behavioral performance and task-based fMRI findings.

1. INTRODUCTION

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Mood disorders are debilitating, often chronic psychiatric conditions. With a 16.5% lifetime prevalence rate in American adults, major depressive disorder (MDD) is the second leading cause of disability and mortality in the world (NIMH, 2013). As evidence of MDD's chronic, recurrent nature, over 70% of individuals with MDD have at least two episodes in their lifetime, but typically as many as 8 to 12 (Kessler, et al., 1997). Approximately 49% of individuals with bipolar disorder (BP) will also experience recurrences (Perlis et al., 2006). Those who experience a recurrence of illness are about twice as likely to experience a depressive episode than manic, hypomanic, or mixed episode (Perlis et al., 2006). Regarding economic impact, BP has been called the most expensive behavioral health diagnosis, and costs the healthcare system twice as much as MDD per individual with the illness (CDC, 2013). Additionally, it is estimated that almost twice as much is spent on inpatient as outpatient care for BP, suggesting that techniques for predicting and preventing recurrence of illness would be extremely useful in decreasing the economic burden of the disease (CDC, 2013). In line with NIMH's strategic plan and the Research Domain Criteria (RDoC) initiative (Insel, et al., 2010), studies on neural and performance-based mechanisms of disease with a dimensional and longitudinal focus can be used to model individual differences in disease course over time,

perhaps increasing our understanding of relapse prediction for these burdensome and debilitating diseases. Furthermore, considering MDD and BP together may enhance our understanding of transdiagnostic or disease-specific mechanisms.

1.1 **Positive Valence System Disruptions in Mood Disorders**

As set forth in the RDoC matrix, the positive valence system is thought to include approach motivation, reward responsiveness, and reward learning. Deficits in reward learning and approach motivation are primarily driven by low reward anticipation (Sherdell et al., 2012; Treadway et al., 2009). Deficits in both reward anticipation and reward consummation manifest as one of the cardinal symptoms of MDD, anhedonia. Anhedonia, which may be experienced in the depressive state of any type of mood disorder, is specific to depression rather than anxiety (Watson et al., 1988a; Clark & Watson, 1991). Anhedonic individuals experience impaired reward learning (Sherdell et al., 2012) and decreased interest in the environment, perhaps because these individuals do not feel reinforced by reward (Costello, 1972; Meehl, 1975). Disrupted reward processing and reward responsiveness (Henriques & Davidson, 2000), then, may be factors that underlie both the development and perpetuation of MDD. Reward processes are also highly disrupted in BP, with affected individuals exhibiting hyperhedonia (i.e., over-reactivity and seeking of reward) during manic or hypomanic episodes and anhedonia during depressive episodes (Pizzagalli et al., 2009).

1.2 **Behavioral Performance Evidence of Reward Disruption in Mood Disorders**

Several aspects of reward processing are disrupted in mood disorders: reward and effort valuation (Treadway & Zald, 2011), reward prediction error (Pizzagalli et al., 2005), preference-based decision-making (Pizzagalli et al., 2008b), and initial and sustained responsiveness to reward (Henriques & Davidson, 2000). Deficits in valuation and anticipation, the “wanting”

phase of reward processing, are commonly observed in MDD and depressive episodes of BP (Berridge & Robinson, 2003; Henriques et al., 1994). The “wanting” phase can also be operationalized as the amount of effort an individual is willing to put in to obtain reward, and willingness to expend effort has been shown to be negatively correlated with anhedonia (Treadway et al., 2009).

Much evidence of dysfunctional reward prediction error and preference-based decision-making comes from probabilistic reward learning paradigms, in which participants must classify ambiguous stimuli as cues for either reward or punishment (Henriques et al., 1994). Response bias is then operationalized as the willingness to classify ambiguous stimuli as reward cues (Henriques et al., 1994). For example, individuals with depressive symptoms show a negative response bias (Henriques et al., 1994), are less able to modulate responses after receiving negative feedback about missing a reward opportunity (Holmes & Pizzagalli, 2007), and have more difficulty acquiring a preference for reward (Pizzagalli et al., 2008b). In a monetary incentive delay task, depressed individuals won less money than healthy individuals at both the beginning and end of the task (DelDonno et al., 2015), indicating aberrant reward learning and reductions in initial and sustained reward responsiveness. Furthermore, trait reward responsiveness was shown to predict MDD individuals’ ability to sustain responsiveness (i.e. accuracy and speed) during a monetary incentive delay task (DelDonno et al., 2015).

Whereas reward sensitivity tends to be blunted in MDD, there is evidence for reward hypersensitivity in BP (Nusslock et al., 2012; Whitton et al., 2015) and other reward learning deficits. These findings offer support for the behavioral activation system (BAS) dysregulation model of BP, which posits that extreme fluctuations in BAS activity lead to marked highs and lows of goal-directed, incentivized behavior (Urosevic et al., 2008). Pediatric patients with BP

have demonstrated specific behavioral deficits with reward learning, such as committing more errors and failing to develop a positive response bias during a probabilistic reward learning task (Gorrdindo et al., 2005). Medicated individuals with BP exhibit worse accuracy than healthy controls (HC) when correctly pursuing an available reward or correctly rejecting an immediate reward in pursuit of later larger reward (Trost et al., 2014), suggesting that individuals with BP are responsive to immediate reward and but may have difficult discriminating exactly when to respond. In support of the idea that individuals with BP are hypersensitive to reward, medicated individuals with BP who were in a current manic, hypomanic, or mixed episode showed no differences in reaction time to trials in which a large reward, small reward, or no reward was available to them (Abler et al., 2008). These same individuals were less accurate and slower than HCs in a monetary incentive task in which receipt of reward was only 60% dependent on participants' accuracy (Abler et al., 2008), which is in contrast to other findings that individuals with BP are generally hypersensitive to reward. Lastly, other studies have shown no differences in reaction time to reward cues between individuals with BP, MDD, or HCs (Redlich et al., 2015). Although these results are tempered by the fact that study participants with BP participate are usually taking psychotropic medications that may be acting on the neurobiological reward system, this mixed literature on reward-related performance highlights the need to investigate this topic further.

1.3 Neural Evidence of Reward Disruption in Mood Disorders

1.3.1 Functional MRI (fMRI) tasks. The ventral striatum (VS) is a primary structure in the reward network that reliably activates during reward anticipation and consummation. When responding to rewards, individuals with active MDD show weaker activation in the nucleus accumbens (NAcc)/VS and caudate relative to HCs (Smoksi et al., 2009; Stoy et al.,

2012; Pizzagalli et al., 2009). Whereas reward-related neural activity in MDD is blunted, this type of neural activity in BP is elevated and hyperactive (Nusslock et al., 2014). BP individuals show elevated activity in the VS, orbitofrontal cortex (OFC), and ventrolateral prefrontal cortex (VLPFC) during reward anticipation but not receipt (Nusslock et al., 2014). Individuals with BP also show increased activation in reward regions such as the ventral tegmental area (VTA), NAcc, and anterior insula to both reward and null trials (Abler et al., 2008), indicating an overactive reward network that is sensitive to non-rewards. As further evidence of overreactivity of the reward system in BP, these individuals showed a smaller difference in NAcc activation when experiencing the receipt versus omission of an expected reward, relative to HCs (Abler et al., 2008). Contrasting research has found that medicated BP individuals showed less activation in midbrain reward regions when pursuing reward, compared to HCs (Trost et al., 2014).

Considering reward network similarities and differences between BP and MDD may help to elucidate transdiagnostic processes. Compared to HCs, individuals with a mood disorder exhibited reduced NAcc activity during a reward-related card guessing game (Redlich et al., 2015) and increased anterior cingulate cortex (ACC) activity relating to reward expectancy (Chase et al., 2013). Across individuals with a mood disorder, depression severity was associated with reduced activation in the VS, ACC, posterior cingulate cortex (PCC), and anterior insula (Satterthwaite et al., 2015), which implies a transdiagnostic endophenotype. Compared to individuals with MDD, those with BP showed reduced activation in several reward network regions (NAcc, caudate nucleus, thalamus, putamen, insula, and PFC; Redlich et al., 2015). However, contrasting studies have reported no differences in VS activation between groups (Chase et al., 2013), again highlighting the lack of consensus on reward network function in mood disorders.

1.3.2 Resting-state connectivity. Resting-state connectivity networks are identified by observing the time course of correlations of spontaneous fluctuations in neural activity across the brain (Biswal, 1995; Fox & Greicius, 2010). Using MRI, it is possible to measure physiological fluctuations in resting-state brain activity by obtaining a time course series of signal intensities of each voxel (Biswal, 1995). Correlations between low-frequency fluctuations in different brain regions represent resting-state networks (Biswal, 1995). Resting-state activity in regions with compatible or similar functionality tends to correlate, thus revealing a network (Fox & Greicius, 2010). Such networks are often characterized by the degree of homogeneity, in that more homogeneity in the spontaneous physiological fluctuations of brain regions represents greater connectivity. Less homogeneity between regions suggests hypoconnectivity, or an anti-correlation between regions (Fox & Greicius, 2010).

Resting-state functional connectivity (rsFC) may “reflect stable trait-like neural characteristics that are independent of and more generalizable than task activation and performance differences” (DelDonno et al., 2017). Examining rsFC may bring clarity to the mixed literature on task-based reward activation in mood disorders.

In mood disorders, there is evidence for decreased connectivity between limbic and cortical structures (Anand et al., 2009). In both MDD and BP, individuals show hypoconnectivity between the pregenual anterior cingulate and the dorsomedial thalamus (Anand et al., 2009). BP individuals exhibit hypoconnectivity from the pregenual anterior cingulate to other regions as well, such as the bilateral amygdala and the left pallidostriatum (Anand et al., 2009). Compared to individuals with BP, individuals with MDD also had stronger connectivity between the NAcc and VTA (Redlich et al., 2015) and greater rsFC within the reward network (Satterthwaite et al., 2015). Across mood disorders, greater depression severity, which is

typically found in BP versus MDD, was associated with reduced reward network rsFC (Satterthwaite et al., 2015). Taken together, it may be that individuals with a mood disorder show more reward network deficits than HCs, but that the reward network in MDD may be more similar to HCs than in BP.

1.4 **Why Study Remitted/Euthymic Mood Disorders?**

We may be better able to disentangle state and trait factors of mood disorders when individuals are in the remitted or euthymic phase of the illness because potentially confounding effects of active symptoms are eliminated (Jacobs et al., 2016), thus potentially allowing for the dissociation of state and trait factors. However, evidence of reward functioning differences between individuals with remitted MDD (rMDD), euthymic bipolar (eBP), and healthy controls (HC) is mixed. Examining reward function in individuals with MDD or BP at three levels of analysis – behavioral performance, task-based fMRI, and resting-state functional connectivity – may clarify mixed findings in the literature and provide new insights into transdiagnostic similarities between MDD and BP, in line with the RDoC (Insel et al., 2010).

1.5 **Reward System Dysfunction in Remitted Mood Disorders**

1.5.1 Behavioral performance. The literature is mixed as to whether reward-related behavioral performance differences exist between individuals with a history of mood disorder compared to HCs. Some studies find no evidence of differences whereas others find deficits similar to those observed in individuals with active illness. Remitted MDD young adults exhibited intact reward pursuit and reward attainment behavior compared to HC, while actively symptomatic MDD individuals showed deficits (DelDonno et al., 2015). Other studies have reported contrasting findings: individuals with rMDD had slower reaction times than HCs during the reward anticipation (Dichter et al., 2012) and failed to develop a response bias towards

rewarding stimuli (Pechtel et al., 2013; Pizzagalli et al., 2008b; Whitton et al., 2015). In the euthymic state, individuals with BP had similar reaction times to HCs during a card guessing reward task (Nusslock et al., 2013) and, like individuals with rMDD, failed to acquire a response bias towards reward in the context of probabilistic learning (Pizzagalli et al., 2008a). In a nonclinical BP sample, greater experience of positive emotions in response to receipt of a monetary reward was linked to higher levels of manic symptoms (Gruber, 2011). Furthermore, individuals with or at risk for BP report higher levels of reward “wanting” (Gruber, 2011). These studies on reward task performance in eBP present mixed findings on reward sensitivity in eBP. Together, it appears that individuals with a history of mood disorder experience reward learning deficits, reward pursuit deficits, and even hypersensitivity to reward. An examination of reward performance across mood disorders in the absence of active symptoms may help to clarify these processes.

1.5.2 Task-based fMRI. Although few studies have examined task-based fMRI correlates of reward function in eBP, there is evidence for heightened reward-related activation in rMDD. Remitted MDD showed hyperactivation relative to HCs during reward anticipation in the bilateral anterior cingulate gyrus, right midfrontal gyrus, and right cerebellum (Dichter et al., 2012). Another study examining neural correlates of reward anticipation found hyperactivation, relative to HCs, in individuals with rMDD in the hippocampus, amygdala, and superior frontal gyrus (Uhl et al., 2015). During the consummation or feedback phase, rMDD individuals exhibited hyperactivation in the bilateral orbital frontal cortex, right frontal pole, left insular cortex, and left thalamus, compared to HCs (Dichter et al., 2012). In a mildly stressful task involving viewing negative emotional stimuli, rMDD participants showed hyperactivation in the caudate, NAcc, and putamen (Admon et al., 2015). Together these findings point

to hyperactivation of the reward network in rMDD individuals during tasks related to the anticipation and experience of reward and negative stimuli.

1.5.3 Functional connectivity. A greater understanding of resting-state connectivity features in individuals with a history of mood disorders, who are by nature at risk for recurrence, may illuminate disease mechanisms, novel treatment targets, and relapse prediction. Networks of interest include the salience and emotion network (SEN) and default mode network (DMN).

The SEN consists of brain areas responsible for salience, affect, and emotion (Seeley et al., 2007). The SEN includes the medial thalamus, amygdala, insula, dorsal anterior cingulate cortex (dACC), and OFC (Seeley et al., 2007), with robust connections to the hypothalamus, NAcc, and other limbic structures (Sheline et al., 2010; Wang et al., 2012). By integrating sensory information with internal and hedonic signals, the SEN functions to facilitate or impede decisions; produce emotional responses to pain, pleasurable music or touch, and reward; and regulate homeostasis (Seeley et al., 2007).

There have been some studies examining SEN connectivity in individuals with mood disorders. Compared to HCs, individuals with rMDD had increased connectivity between the anterior insula, posterior insula, and supramarginal gyrus, while number of depressive episodes trended towards a significant correlation with posterior insula connectivity (Guo et al., 2015). In young adults with rMDD, left amygdala showed hyperconnectivity with the right medial frontal gyrus, medial parietal lobe, rostral ACC, and left parahippocampal gyrus, which demonstrated increased SEN connectivity in individuals with rMDD relative to HCs (Jacobs et al., 2014). In adults with rMDD, hyperconnectivity was observed from the caudate to the amygdala and hippocampus (Admon et al., 2015). In contrast, amygdala hypoconnectivity with the superior VS accurately classified rMDD participants versus HC (Bhaumik et al., 2016). Compared to HCs,

individuals with BP exhibited decreased connectivity between the amygdala and VLPFC (Townshend et al., 2013) and aberrant within-SEN connectivity (Mamah et al., 2013). These findings point to the amygdala and insula as important SEN regions in mood disorders. Overall, the extant literature provides evidence for within-SEN hyperconnectivity and increased connectivity from the SEN to other brain regions in individuals with mood disorders relative to healthy comparisons (Jacobs et al., 2014; Admon et al., 2015; Price et al., 2017). However, a lack of consensus in the definition of the SEN limits conclusions that may be drawn about the role of the SEN in mood disorders, and there are only a few studies of the SEN in remitted/euthymic mood disorders. The present study seeks to clarify SEN function in remitted/euthymic mood disorders, using a relatively broad definition of the network that includes both salience and emotion processing regions.

While many previous studies of mood disorders have observed connectivity alterations in the SEN, others have focused on the default mode network (DMN). The DMN is thought to consist of the PCC, medial prefrontal cortex (MPFC), ACC, and the medial, lateral, and inferior parietal cortices (Greicius et al., 2007; Jacobs et al., 2014; Raichle et al., 2001; Wang et al., 2012). Preschoolers with a history of depression showed increased connectivity between the PCC and MPFC but reduced connectivity between PCC and lateral cortical regions (Gaffrey et al., 2012), suggesting altered connectivity between the PCC and other core DMN regions. Hyperconnectivity of the PCC and subgenual cingulate with lateral, parietal, and frontal regions was observed in young adults with rMDD (Jacobs et al., 2014). In fact, a machine-learning algorithm was able to differentiate rMDD from HC participants based on heightened resting-state connectivity between the left PCC and DLPFC (Bhaumik et al., 2016). These findings point to increased within-DMN connectivity in individuals with depression compared to HCs. Meta-

analyses have offered further evidence of increased resting-state functional connectivity within the DMN in MDD individuals compared to HC (Kaiser et al., 2015; Hamilton et al., 2015).

Alterations in network homogeneity of the DMN in first-episode medication-naïve individuals with MDD has also been observed, with a previous study reporting increased network homogeneity in the left dorsal medial PFC and increased network homogeneity in the right inferior temporal gyrus, relative to HCs, although the network homogeneity values were not correlated with clinical variables (Guo et al., 2014). Increased regional homogeneity has been observed in some DMN regions (left medial frontal gyrus and left inferior parietal lobe) in individuals with bipolar disorder compared to HCs (Liu et al., 2012). Although more research is needed and the current literature is somewhat mixed, the existing findings on network homogeneity point to increased DMN resting-state homogeneity in individuals with mood disorders relative to HC. More studies of SEN homogeneity in mood disorders are needed.

In considering the relationship between SEN and DMN connectivity, hyperconnectivity within a ventral affective network (including the amygdala, NAcc, insula, ventral lateral PFC, and subgenual ACC) during a positive mood induction task predicted MDD status and decreased DMN resting-state connectivity (Price et al., 2017). In adolescents with major depression, there was increased connectivity from the left amygdala to parietal cortex and decreased connectivity from the right amygdala to ACC and occipito-parietal areas, signifying lateralized altered DMN connectivity to brain regions within the SEN (Pannekoek et al., 2014). During a task that elicited externally-focused attention, another group reported greater DMN connectivity and reduced SEN connectivity in individuals with MDD compared to HCs (Belleau et al., 2014). Children with BP were found to have greater functional connectivity between the DMN and SEN, but no evidence of heightened within-network connectivity (Lopez-Larson et al., 2017). Taken together, much of

the existing literature points to increased DMN-SEN connectivity in individuals with mood disorders.

1.6 Moderators and Mediators of Symptom Course

Naturalistic course tells us a great deal about severity, morbidity, and functional impact of disease, including recurrence. In the absence of treatment, the majority of individuals with mood disorders experience a chronic and recurrent course of illness. For example, adolescents with MDD experienced affective symptoms at an annual rate of 9% as they progressed into adulthood, compared with affective symptoms at 3.7% annually for adolescents with no disorder (Lewinsohn et al., 1999). In a 10-year prospective longitudinal study, individuals with chronic depression or dysthymia remitted at a rate of 73.9% but had a 71.4% risk of relapse (Klein et al., 2006). In a 12-year prospective longitudinal study, individuals with BP were symptomatically ill for 47.3% of weeks, with depressive symptoms being more common than manic or hypomanic symptoms (Judd et al., 2002). One study reported that even for individuals with MDD who received a course of treatment, 19%-30% relapsed within 18 months of concluding treatment (Shea et al., 1992).

Although much research to date has identified stress as a risk or exacerbating factor for mood symptoms (DeLongis et al., 1988; Carlson et al., 2003), few studies have investigated potential moderators and mediators of symptom fluctuation and naturalistic course of illness in mood disorders. In a non-clinical adolescent sample, effortful control moderated and ruminative response style mediated depressive symptoms over one year (Verstraeten et al., 2009). Other moderators may include gender, early life adversity, and social support, while other mediators may include interpersonal deficits, negative cognitive style, and poor coping (Boland et al., 2002). Predictors of treatment response in MDD may include ACC, MPFC, and amygdala

activation, given that these regions are involved with implicit emotion regulation (Phillips et al., 2015). However, few if any studies have evaluated aspects of reward functioning and/or the positive valence system as potential moderators or mediators of course of illness.

Elucidating moderators and mediators of naturalistic symptom fluctuation may provide novel avenues for relapse prediction or intervention. For instance, if an affective trait predicted variability in mood symptoms over time, clinicians might be able to use a brief self-report to predict which of their patients would need booster sessions following a course of psychotherapy. Similarly, if performance on a reward task mediated the relationship between disease state and level of depressive symptoms, patients themselves might be able to self-administer the task and determine whether their performance indicates that they should seek professional help or increase engagement in coping techniques. It may even be possible to use extracted brain activation values or patterns of network activation to identify patients at high risk for relapse. While relationships between reward functioning metrics and clinical outcomes may be not be so one-to-one and linear, attempting to understand predictors of naturalistic symptom fluctuation and relapse has value for the field in personalized precision medicine.

1.7 Aims of the Present Study

Few studies have evaluated and directly compared self-report, task, and neural facets of reward functioning in a combined sample of rMDD and eBP individuals. This study aimed to add a greater understanding of transdiagnostic reward processes using a dimensional, multimodal approach. The current project addressed a lack of research into mediators and moderators of naturalistic symptom fluctuation. A greater understanding of these trait and state mechanisms could increase our ability to predict relapses in mood disorders, which are, unfortunately, common and frequent. Furthermore, using a sample of individuals with a history of mood

disorders but not active symptoms helped us examine trait moderators of symptom fluctuation, in that confounding effects of active symptoms were diminished. Results of the current study may enhance our understanding of approach motivation, performance, and neural predictors of symptom fluctuation and relapse in mood disorders, in line with RDoC (Table I).

Aim 1. Evaluated between-group differences in reward functioning and network connectivity.

Hypothesis 1. Compared to HCs, participants with a history of mood disorder (HMD) would have lower trait positive affect, worse performance on reward processing tasks, increased connectivity from key regions in the reward circuit to the SEN and DMN, and more homogeneity in the DMN and less in the SEN. These expected results would be in line with previous research that has found deficits in reward system function in individuals with MD or BP compared to HC.

Aim 2. Evaluated whether baseline self-reported reward responsiveness, a facet of trait positive affect, predicted fluctuations in mood symptoms over time in the HMD group or moderated the effect of diagnosis on mood symptoms over time.

Hypothesis 2. Individuals with lower baseline reward responsiveness would have greater variability in mood symptoms over time. These expected results would suggest that low trait positive affect is a vulnerability factor for increased mood variability and relapse, and would suggest that positive affect is a moderator of naturalistic symptom fluctuation.

Aim 3. Explored whether reward task performance predicted depressive symptom change over time on the individual level for participants in the HMD group.

Hypothesis 3. Better reward task performance would predict lower depression scores in a lagged manner over time. These expected results would suggest that the ability to pursue and attain reward, i.e. heightened reward responsiveness and anticipation, is a mediator of naturalistic symptom fluctuation.

2. METHODS

(Parts of this chapter were previously published in DelDonno, S. R., Weldon, A. L., Crane, N. A., Passarotti, A. M., Pruitt, P. J., Gabriel, L. B., ... & Langenecker, S. A. (2015). Affective personality predictors of disrupted reward learning and pursuit in major depressive disorder. *Psychiatry research*, 230(1), 56-64. [PMCID: PMC4601921]; and DelDonno, S. R., Jenkins, L. M., Crane, N. A., Nusslock, R., Ryan, K. A., Shankman, S. A., ... & Langenecker, S. A. (2017). Affective traits and history of depression are related to ventral striatum connectivity. *Journal of affective disorders*, 221, 72-80.)

2.1 Participants

The Multifaceted Explorations of the Neurobiology of Depressive Disorders Laboratory in the Cognitive Neuroscience Center at the University of Illinois at Chicago recruited young adults ages 18-30 with and without a history of mood disturbance. These individuals participated in a larger parent RDoC study of negative mood systems that consisted of two laboratory visits. For the current study, all individuals who successfully completed both visits were re-contacted and, if interested, enrolled in the current study procedures.

Participants in the history of mood disturbance group (HMD, $n = 132$) had experienced at least one week or more of mood disturbance in the past. Mood disturbance was defined as diagnoses of MDD, BP, and mood NOS categories, as well as subthreshold presentations of those disorders. Subthreshold major depressive episode was defined as meeting at least four out of nine diagnostic criteria for at least two weeks in the past or meeting five or more diagnostic criteria for at least one week in the past. Subthreshold BP was defined as meeting criteria for at least one subthreshold major depressive episode in the past as well as meeting criteria for at least one past hypomanic episode. Of those in the HMD group, 105 (80%) individuals met full or

subthreshold DSM-5 criteria for past MDD, 21 (16%) individuals met full or subthreshold criteria for past bipolar I disorder, and 6 (5%) individuals met full or subthreshold criteria for past bipolar II disorder. The large majority of individuals with HMD were enrolled in the remitted/euthymic phase of illness, scoring 8 or below on the Hamilton Rating Scale for Depression (HAM-D). However, 11% of the HMD sample had HAM-D scores ranging from 9 to 21 at the time of enrollment. Comorbid anxiety disorders were permitted for enrollment in the HMD group; 4% of the HMD group scored from 17 to 23 on the Hamilton Anxiety Rating Scale, indicating moderate anxiety. HMD participants had HAM-D and Young Mania Rating Scale (YMRS) scores less than 8 at the time of enrollment. Those with stable psychotherapy over the four weeks prior to enrollment were eligible (6% of HMD sample). If potential participants were currently using psychostimulants, benzodiazepines, sleep aids, or pain medications, they were asked to refrain from taking medications one day before and the day of any study visits. Those who did not agree were not enrolled.

Individuals in the healthy control (HC) group had no personal or family history of any psychiatric problems. One participant who was enrolled as a healthy control reported experiencing a subthreshold major depressive episode during the follow-up period and was therefore excluded from all analyses, resulting in a HC group of $n = 43$. Table II presents the demographic and clinical information for the sample.

Exclusionary criteria included significant, active substance abuse in the last month or dependence in the last two years; change in treatment status within the last month (e.g. new provider, new treatment); psychotropic medication use in the 4 weeks prior to study enrollment; current antipsychotic medication use; history of psychosis outside of severe manic episodes; chronic or serious medical conditions known to affect cognitive functioning and/or mood; history

of a developmental disability, neurocognitive disorder, or traumatic brain injury; an active suicidal plan or history of serious suicide attempt in the last six months; contraindications for fMRI; pregnancy; status as a prisoner or institutionalized individual.

Safety protocols were in place in case of any participant or potential participant reporting active suicidal ideation, but never needed to be utilized.

2.2 Procedures

All study procedures were approved by the University of Illinois at Chicago Institutional Review Board and conducted in accordance with the Declaration of Helsinki. In the parent RDoC study, participants completed Time 1 and Time 2 visits. The study procedures reported here constituted Time 3.

Individuals in the community responded to recruitment materials for the RDoC study and were contacted by phone for an eligibility screening. During the phone screening conducted by a trained research assistant, participants heard a detailed description of the study and were given the chance to ask questions. If eligible and interested, participants were invited to the laboratory for a baseline assessment. After obtaining informed consent and confirming eligibility (approximately 30-45 minutes), participants completed a 2.5-hour baseline clinical assessment. In the clinical assessment, a trained Masters-level clinician conducted a version of the Structured Clinical Interview for DSM-IV (SCID; First et al., 1995) that was modified to provide a dimensional, rather than categorical, assessment of symptoms and diagnosis, in the spirit of RDoC. A small subset of participants at the start of the study were diagnosed using the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994), prior to switching to the dimensional SCID (Shankman et al., 2018).

At Times 1 and 2, participants underwent an fMRI scan, neuropsychological testing, clinician assessments, and self-report questionnaires. The fMRI session included structural, resting-state, and functional scans. The Monetary Incentive Delay Task (described below) was administered both outside and then inside the scanner. A subset of the clinician assessments and self-report questionnaires, which were repeated at Time 3, measured mood symptoms, anxiety, and positive and negative affect. Participants who completed two visits in the parent study were re-contacted via email to invite them to participate in Time 3. The Time 3 visit, lasting about 1.5 hours, consisted of one computerized task, several brief self-report questionnaires, and several clinician-administered assessments. Participants were compensated \$50 for the Time 3 visit.

At Time 1, participants were 132 individuals with HMD and 43 HCs. Time 2 comprised 46 individuals with HMD and 17 HCs. Number of days between Time 1 and Time 2 did not differ between the HMD group ($M = 333$, $SD = 227$) and HC group ($M = 318$, $SD = 326$), $t = -.18$, $p = .86$. Of the participants who completed Time 2 who were then invited to complete Time 3, 24% of the HC participants and 28% of the HMD participants either declined, did not respond, did not complete the scheduling process, or had moved out of state. Time 3 comprised 33 individuals with HMD and 13 HCs. Number of days between Time 2 and Time 3 was significantly different for the HMD group ($M = 408$, $SD = 74$) and HC group ($M = 260$, $SD = 122$), $t = -5.06$, $p < .001$. Number of days between Time 1 and Time 3 did not differ between the HMD group ($M = 741$, $SD = 280$) and HC group ($M = 577$, $SD = 276$), $t = -1.79$, $p = .08$.

2.3 Measures

2.3.1 Behavioral reward functioning. The Monetary Incentive Delay Task (MIDT) was used to assess reward functioning. The following description has previously been published in our earlier work (DelDonno et al., 2015; DelDonno et al., 2017). In the MIDT, “participants

responded to a simple visual stimulus (target) with an index-finger button-press within a predefined response window” (DelDonno et al., 2015; DelDonno et al., 2017). The present task was modified from the original task (Knutson et al., 2000) and presented in E-Prime (Version 2.0, Psychology Software Tools Inc., Pittsburgh PA, USA). “There were three types of trials: win, neutral, and loss trials. At the beginning of each trial, the type of trial upcoming and amount of money at stake was indicated by a cue: ‘win \$5’ or ‘win \$0.20’ in a red circle, ‘don’t lose \$5’ or ‘don’t lose \$0.20’ in a blue square, or ‘no money at stake’ in a green triangle. The cue then disappeared and, after a variable delay, a white square (the target) flashed on the screen. Upon seeing the target, participants were instructed to press the button as quickly as possible within the response window in order to win \$0.20 or \$5 (on win trials) or avoid losing \$0.20 or \$5 (on loss trials). On neutral trials, no money was at stake, no matter how quickly participants responded; however, participants were instructed to respond as quickly as possible even on neutral trials. After the target disappeared, participants received feedback as to whether they won or lost money” (DelDonno et al., 2015; DelDonno et al., 2017). The three types of trials yielded nine possible outcomes: \$0.20 or none earned (small win trials), \$5 or none earned (big win trials), none lost or -\$0.20 (small loss trials), none lost or -\$5 (big loss trials), or no money at stake (\$0). The jittered inter-trial interval (ITI) ranged from 2000-6000 ms with an average duration of 4000 ms. The task consisted of four runs of 25 trials each (5 per type) and lasted about 24 minutes (6 minutes per run). The order of trial types was randomized within each run. An example trial showing the timing of the task is presented in Figure 1.

“Before completing runs 1-4, participants completed a 25-trial baseline run outside of the scanner. Besides acquainting participants with the task, the purpose of the baseline run (with a fixed 250 ms response time) was to measure each participant’s reaction time (RT) to the target

stimulus and then titrate the in-scanner task to that individualized response window. For example, if a participant's average RT to the target during the baseline run were 220 ms with a standard deviation (SD) of 30 ms, the response window for run 1 would be set to 265 ms (mean plus $1.5 \times \text{SD}$). Titration adjustments were also made after the first and second runs of the task based upon number of correct responses, which was tracked by the experimenter and kept blind to the participant. Response window durations were either increased or decreased by .5 SD of the baseline average RT if accuracy was below 50% or above 80%, respectively. Participants were told that only their performance on runs three and four would count towards their total earnings (up to \$52 more than the base compensation) and that no money would be taken away if their final performance was below \$0. The individual titration process was aimed to result in each participant achieving 50-80% accuracy on the task. Titration also standardized the task by removing the effect of each participant's individual psychomotor ability" (DelDonno et al., 2015; DelDonno et al., 2017).

The task was administered during the fMRI scan at Time 1 and during the neuropsychological batteries at Times 1, 2, and 3.

Across groups, participants earned -\$10.20 to \$52 (range of \$62.20) outside the scanner and -\$26.40 to \$52 (range of \$78.40) in the scanner. Healthy control participants earned \$15.40 to \$52 (range of \$36.30) outside the scanner and -\$26.40 to \$46.40 (range of \$72.80) in the scanner. Participants in the HMD group earned -\$10.20 to \$52 (range of \$62.20) outside the scanner and -\$21.20 to \$52 (range of \$73.20) in the scanner.

Intraclass correlation coefficient (ICC) estimates and their 95% confidence intervals were calculated in SPSS based on a single-rating, absolute agreement, two-way random effects model. In the whole sample over the three assessment time points, ICC for amount of money won during

runs 3 and 4 of the MIDT (AMW) was .35, with a 95% confidence interval of .17-.54, indicating poor-to-moderate reliability. In the HC group across time points, ICC for AMW was .30, with a 95% confidence interval of -.05-.67, indicating poor-to-moderate reliability. In the HMD group, ICC for AMW was .36, with a 95% confidence interval of .14-.57, indicating poor-to-moderate reliability.

2.3.2 Measures of mood and anxiety symptoms.

Beck Depression Inventory (BDI). The BDI (Beck et al., 1996) is a self-report measure of depressive symptoms over the last two weeks. In the whole sample over the three assessment time points, ICC was .79, with a 95% confidence interval of .68-.87, indicating moderate-to-good reliability. In the HC group, ICC across the three time points was .22, with a 95% confidence interval of -.13-.63, indicating poor-to-moderate reliability. In the HMD group across the three time points, ICC was .73, with a 95% confidence interval of .57-.84, indicating moderate-to-good reliability.

Beck Anxiety Inventory (BAI). The BAI (Steer & Beck, 1997) is a 21-item self-report measure of broad anxiety symptoms over the last week.

Hamilton Rating Scale for Depression (HAM-D). The HAM-D (Hamilton, 1960) is a 17-item clinician-administered assessment of current depressive symptoms. Widely used today in both clinical and research settings, it measures depressive mood and cognitions (low mood, guilt, suicidality), anhedonia, and somatic depression (changes in appetite, sleep, psychomotor features).

Hamilton Rating Scale for Anxiety (HAM-A). The HAM-A (Hamilton, 1959) is a well-validated clinician-administered assessment of current anxious symptoms. Widely used today in both clinical and research settings, it measures psychic anxiety (mental agitation and

psychological distress), and somatic anxiety (physical symptoms of anxiety).

Young Mania Rating Scale (YMRS). The YMRS (Young et al., 1978) is a clinician-administered evaluation of current manic symptoms, assessed through explicit questions to the participant and behavioral observations. In the whole sample over the three assessment time points, ICC was .55, with a 95% confidence interval of .37-.72, indicating poor-to-moderate reliability. In the HC group, ICC across the three time points was <.01, with a 95% confidence interval of -.28-.47, indicating poor reliability. However, at each time point a majority of the YMRS scores in the HC group were 0 (see Figure 3), and the resulting lack of variance explains the very low ICC. In the HMD group across the three time points, ICC was .44, with a 95% confidence interval of .21-.67, indicating poor-to-moderate reliability.

2.3.3. Measures of anhedonia and affect.

Snaith-Hamilton Pleasure Scale (SHAPS). The SHAPS (Snaith et al., 1995) measures anhedonia.

Temporal Experience of Pleasure Scale (TEPS). The TEPS (Gard et al., 2006) measures the experience of anticipating and receiving a reward/pleasure. Due to the study protocol being retrospectively amended to include more reward-related measures, the TEPS was only administered at time 3.

Positive and Negative Affect Scale (PANAS). The PANAS (Watson et al., 1988b) measures current positive affective and negative affective state.

Behavioral Inhibition Scale/Behavioral Activation Scale (BIS/BAS). The BIS/BAS (Carver & White, 1994) is a 20-item self-report measure that assesses trait avoidance (trait negative affect) and trait approach motivation (trait positive affect). The measure has four subscales: behavioral inhibition, reward responsiveness (BAS-RR), drive, and fun-seeking. BAS-

RR was the only subscale used in analyses. The BIS/BAS was completed only at Time 1.

2.4 Statistical Analyses

Prior to analyses, all variables were checked for unusual datapoints or distributions and the validity of underlying statistical assumptions (e.g. skewness, sphericity).

2.4.1 Aim 1. First, we evaluated differences in reward functioning and network connectivity between the HMD and HC groups. Analyses for Aim 1 represent the Time 1 sample size. Individual samples t-tests were used to assess group differences in MIDT behavioral performance (accuracy, reaction time, amount of money won) and self-report questionnaires on state anhedonia, trait reward-responsiveness, state positive and negative affect. Brain activation during reward anticipation in the MIDT and resting-state connectivity between key reward circuit regions and the SEN and DMN were compared between groups.

fMRI preprocessing. Functional and resting-state images were slice-time corrected with SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/doc/>) and motion corrected with FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). Structural and functional images were co-registered. Spatial normalization (DARTEL to MNI template) was performed on the co-registered T1-MPRAGE. The resulting normalization matrix was then applied to the slice-time-corrected, movement-corrected time series data and smoothed with a 5 mm Gaussian kernel. Resulting T2* images contained were 2 mm isotropic voxels.

Movement correction. Images were visually inspected for movement greater than 1.5 mm on the pitch, yaw, or roll axes across more than three consecutive TRs. For MIDT analyses, one HC and four HMD (three rMDD, one eBP) participants were excluded for having more than two runs with excessive movement. For connectivity analyses, after the first-pass visual movement check, we excluded six HC and 13 HMD (nine rMDD and four eBP) participants

because more than 20% of the sums of the absolute values of the six FSL-generated movement parameters exceeded .5, a rule that was based on considerations raised by Power et al., 2014.

Task-based fMRI model. A contrast of interest was created by subtracting BOLD (blood oxygen level dependent) signal during neutral trial from win trial BOLD signal (W-N). This contrast was not based on actual performance, so win trial activation encompassed the anticipation of potential wins. A between-groups ANOVA was conducted with W-N activation as the dependent variable. Covariates of no interest were age, sex, and the average standard deviations of pitch, roll, and yaw translations. The model included an explicit gray matter mask. We used the bug-fixed 3dClustSim tool (Cox et al., 2016) to determine cluster extent from 1000 Monte Carlo simulations, resulting in a joint threshold of height and extent ($p < .005$, extent of 464 mm³). The Monte Carlo approach aimed to balance Type I and Type II error. Whole brain alpha of .01 was achieved.

Cross-correlation connectivity analysis (rsFC). The following description of the cross-correlation analysis procedures was previously published (DelDonno et al., 2017). Time series was detrended and mean centered. Physiologic correction was performed by regressing out mean signal from white matter and cerebral spinal fluid (Behzadi et al., 2007). Motion parameters and deviations in x, y, and z translation were regressed out within first level models (Jo et al., 2013). Global signal was not regressed due to collinearity violations with gray matter signal, problematic misestimates and introductions of anticorrelations (Fox et al., 2013), and effect on distance-micromovement relationships (Jo et al., 2013). Finally, time-series were band-pass filtered over 0.01–0.10 Hz.

Seeds of interest and MNI coordinates, as displayed in Figure 2, were the left VSs (-10, 15, 0; Di Martino et al., 2008), right VSs (10, 15, 0; Di Martino et al., 2008), left VSi (-9, 9, -8;

Di Martino et al., 2008), right VSi (9, 9, -8; Di Martino et al., 2008), left amygdala (-23, -5, -19; Jacobs et al., 2016), right amygdala (23, -5, -19; Jacobs et al., 2016), left dorsolateral prefrontal cortex (DLPFC, -41, 55, -4; Yeo et al., 2011), right DLPFC (41, 55, -4; Yeo et al., 2011), left dorsal anterior cingulate cortex (dACC, -5, 22, 47; Yeo et al., 2011), and right dACC (5, 22, 47; Yeo et al., 2011). These spherical ROIs comprised 19 voxels (6x6x6 mm sphere) each.

A 2 (group) x 2 (side) x 5 (seed) multifactorial ANOVA was built in SPM8 with age, sex, and average standard deviations of pitch, roll, and yaw translations entered as covariates of no interest. Spatially averaged time course data were modeled from this group of ROIs in cross correlation analyses. “Correlation coefficients between mean time course for the ten seed regions and all other voxels of the brain were calculated, producing a three-dimensional correlation coefficient r image for each seed” (Jacobs et al., 2014; Jacobs et al., 2016; DelDonno et al., 2017). “ R images were transformed to z -scores using a Fisher transformation” (Jacobs et al., 2014; Jacobs et al., 2016; DelDonno et al., 2017). In MarsBaR (Brett et al., 2002), we applied a DMN mask and extracted values that represented the connectivity between each seed region and the DMN; we repeated this procedure with an SEN mask. To simplify further analyses, we averaged the extracted values by seed and side so that we could examine between-groups differences in connectivity between all reward circuit ROIs and the DMN, all ROIs and the SEN, left side ROIs and DMN, right side ROIs and SEN, bilateral VSs to DMN, bilateral VSs to SEN, bilateral VSi to DMN, bilateral VSi to SEN, bilateral DLPFC to DMN, bilateral DLPFC to SEN, bilateral amygdala to DMN, bilateral amygdala to SEN, bilateral dACC to DMN, and bilateral dACC to SEN. The reward seeds, SEN, and DMN are displayed in Figure 4.

To assess reward node to network homogeneity, standard deviations of the connectivity value between each seed and a DMN or SEN mask were pooled, producing a pooled standard deviation of connectivity between all the reward seeds and either the DMN or SEN.

2.4.2 Aim 2. In SAS, using the generalized estimating equation method with exchangeable correlation matrix, we evaluated whether baseline self-reported reward responsiveness predicted change in mood symptoms over time. BAS-RR was the fixed predictor and either YMRS or BDI was the time-varying dependent variable. Group and number of days between visits were covariates. BAS-RR, YMRS, and BDI were z-scored prior to analyses. BDI and YMRS distributions were inspected for skew and were subsequently log-transformed due to right skewedness (see Figure 3 for display of YMRS scores before transformation). We ran separate models with YMRS or BDI as the dependent variable. Since not all Time 2 participants completed Time 3, these models represent the Time 2 sample size with some missing data in Time 3.

2.4.3. Aim 3. In SAS, using a path analysis with maximum likelihood estimation, we explored whether amount won (AMW) in runs 3 and 4 of the MIDT predicted self-reported depressive symptoms (BDI scores) from one time point to the next, in the HMD group. Three BDI scores and three AMW values (from each time point) were entered into the model. Since not all Time 2 participants completed Time 3, these models represent the Time 2 sample size with some missing data in Time

3. RESULTS

3.1 Self-Report and Behavioral Reward Functioning

Table III presents the group differences on self-report and behavioral measures of affect and reward function across the three time points. At time 1, the HMD group reported significantly less state positive affect and more state negative affect (PANAS) than the HC group. The HMD group reported significantly greater state anhedonia (SHAPS) than the HC group at time 1 and 3. At time 3, the HMD group had significantly lower scores than the HC group on the consummatory subscale of the TEPS. For the MIDT at all assessments, there were no behavioral differences between groups on amount of money won, win and neutral trial accuracy, and win and neutral reaction time. For the reader's interest, we also present quantitative statistics for the rMDD and eBP group comparisons on key reward, affect and symptom measures (Table IV).

3.2 BOLD Response During Reward Anticipation

Clusters of activation during the MIDT are presented in Table V. Participants in the HC group exhibited greater activation in the decline than the HMD group during anticipation of win trials compared to anticipation of neutral trials. There were no areas of greater activation in the HMD compared the HC group. Across groups, wide bilateral activation was observed during anticipation of win trials relative to neutral trials, including in the cingulate, caudate, insula, putamen, all frontal gyri, precentral and postcentral gyri, superior temporal gyrus, cerebellum, and occipital regions (Figure 5).

3.3 Resting-State Network Connectivity

Group differences in connectivity from the reward circuit to the SEN and DMN are presented in Table VI. In the HMD group compared to HC group, there was decreased

connectivity from the bilateral amygdala ($t = 2.00, p = .048$) and bilateral dACC ($t = 2.06, p = .04$) to the average cross-network connectivity of the DMN. There was increased connectivity from the right-sided reward regions (VSs, VSi, amygdala, DLFPC, and dACC) to the average connectivity of the SEN, $t = -2.60, p = .01$, in the HMD group compared to HC. The bilateral amygdala had increased connectivity to the average of the SEN in the HMD compared to HC groups, $t = -6.49, p < .001$, whereas the bilateral dACC showed reduced connectivity to the average of the SEN in the HMD group compared to HC group, and $t = 2.77, p = .01$.

Connectivity between the reward network ROIs, which included regions in the SEN, and SEN was lower in the HMD group compared to HC group, whereas cross-network reward-DMN connectivity did not differ between groups (Table VI). Reward-SEN and reward-DMN connectivity did not differ between the HC, rMDD, and eBP groups. Across groups, reward-SEN and reward-DMN connectivity were significantly correlated, $r = .78, p < .001$, with covariance = .002. In the HC group, reward-SEN and reward-DMN connectivity were significantly correlated, $r = .83, p < .001$, with covariance = .002. In the HMD group, reward-SEN and reward-DMN connectivity was significantly correlated, $r = .75, p < .001$, with covariance = .001.

3.3.1 Network homogeneity. In the HC compared to HMD groups, Levene's tests for homogeneity of variances in the reward-SEN (Levene statistic = 1.12) and reward-DMN (Levene statistic = .03) were non-significant for both networks, p 's $< .10$. Comparing the HC to rMDD to eBP groups, Levene's tests for homogeneity of variances in the reward-SEN (Levene statistic = .56) and reward-DMN (Levene statistic = .32) were both non-significant, p 's $< .10$.

The pooled standard deviation of connectivity between the DMN and the reward seed regions was non-significantly greater in the HMD group ($M = .57, SD = .05$) than the HC group ($M = .55, SD = .05$), $t = -1.92, p = .06$. The pooled standard deviation of connectivity from the

reward seed regions to the SEN did not differ between the HMD group ($M = .60$, $SD = .05$) and the HC group ($M = .59$, $SD = .06$, $t = -.80$, $p = .43$).

3.4 Trait Reward-Responsiveness and Mood Symptom Fluctuation

Depression and mania scores at each time point for both groups are presented in Table VII.

3.4.1 Predicting depression symptoms. Baseline BAS-RR did not predict BDI scores over time, whereas group significantly predicted BDI scores such that the HC group had lower scores than the HMD group (Table VIII, Figure 6). In a model with the HMD group only, no significant predictors of BDI scores emerged (Table VIII).

3.4.2 Predicting mania symptoms. Baseline BAS-RR did not predict YMRS scores over time, whereas group and the interaction of group and BAS-RR over time did significantly predict YMRS scores (i.e., low BAS-RR predicted increasing YMRS scores in the HMD group only over time, Table VIII, Figure 7). In a model with the HMD group only, no significant predictors of YMRS scores emerged (Table VIII).

3.5 Behavioral Reward Performance and Mood Symptom Fluctuation

In the HMD group, baseline performance on MIDT did not predict change in BDI scores over time. BDI at time 1 predicted BDI at time 2, BDI at time 2 predicted BDI at time 3, and AMW at time 2 predicted AMW at time 3 (Table IX).

4. DISCUSSION

The current study examined multimodal reward functioning in individuals with a history of mood disturbance compared to individuals with no psychiatric history and aimed to predict changes in mood symptoms over time from self-report and objective measures of reward-responsiveness.

4.1 Self-Reported and Behavioral Reward Functioning

At baseline, the HMD group reported less state positive affect and more state negative affect than the HC group. Previous studies found greater depressive symptoms in individuals with remitted depression compared to healthy controls, despite the level of symptomology still being low enough to be considered remitted (Pechtel et al., 2013). Another study found that individuals with remitted MDD reported more negative affect compared to never-depressed individuals, although found no group differences in positive affect (Bagley et al., 2011). On the other hand, another study found no differences in positive or negative affect for rMDD individuals compared to healthy controls (Vanderhasselt et al., 2012). The mean scores for positive affect reported in that study appear similar to those in the current study, and it may be that the study by Vanderhasselt and colleagues, which had fewer than 20 participants in each group, was underpowered to find significant group differences in positive affect. Our sample included those with any level of anxiety at baseline, which could explain the higher state negative affect (Watson et al., 1988a).

At baseline and the final follow-up visit, the HMD group reported more state anhedonia than the HC group. Intuitively it makes sense for individuals with lower state positive affect to also report greater state anhedonia. State anhedonia was not measured at Time 2, but it may be that individuals with a history of mood disorder have slightly elevated anhedonia as a trait

feature. In fact, a study of participants with eBP and rMDD found that the clinical group had higher SHAPS scores compared to HCs (Di Nicola et al., 2013). Elevated anhedonia has also been reported as a feature of prodromal bipolar disorder (Alloy et al., 2009). The HMD group reported less of a trait disposition to consummatory experiences of pleasure, compared to the HC group, at Time 3. Trait anhedonia was not assessed at Times 1 and 2 due to the current study protocol being added on to an existing project, so the current data do not speak to the relationship between naturalistic symptom fluctuation and trait anhedonia. With anhedonia being a cardinal feature of depression, the consistently higher BDI scores in the HMD group, compared to HC, could explain the heightened anhedonia at various points throughout the study.

There were no behavioral group differences on AMW during the MIDT at any time point. Many studies do not find (Knutson et al., 2001; Knutson et al., 2008; Andrews et al., 2011; Jia et al., 2011; Balodis et al., 2012) or may not report group behavioral differences on the MIDT (Knutson et al., 2000; Patel et al., 2013). Lack of performance differences between the clinical group and healthy comparison group is in keeping with the original intent of the task, which was to elicit NAcc activation in the absence of behavioral performance differences (Knutson et al., 2000; Balodis & Potenza, 2015). Although the MIDT may be sensitive to behavioral deficits in participants in the active phase of MDD (DeDonno et al., 2015), the task may not detect or there may not be behavioral reward responsiveness deficits in individuals in the remitted or euthymic phase of illness. At the same time, lack of performance differences indicates that our titration procedure was successful in removing the effects of individual psychomotor differences and equalizing performance between groups. It should also be noted that in this experiment (at Time 1), the MIDT was completed in the neuropsychological evaluation prior to completion within the scanner, and the numerical value of AMW was nonsignificantly lower in the HMD group than

the HC group. In our previous paper (DeDonno et al., 2015), the scanner version was the only exposure to the MIDT task, and it was completed in the scanner for the active MDD group. Direct, cross-lagged comparisons of MIDT performance across phases of illness are still needed to directly determine whether it is a trait- or state-influenced measure. Baseline performance on MIDT did not predict change in BDI scores over time.

4.1.1 Impact of residual symptoms on task performance

It is important to consider the extent to which, even in remission, residual depressive symptoms distort our ability to identify trait markers of illness. Many studies have reported lingering impairment in cognitive function, such as working memory (Hoorelbeke et al., 2016), attention (Vives et al., 2015), and inhibitory control (Aker et al., 2016), in individuals with remitted MDD compared to HCs. These studies note that cognitive performance did improve in remission relative to active illness, but not to the level of the never-depressed comparison participants. A similar pattern of deficits has also been observed in affective and social cognitive domains. After treatment with citalopram, individuals with MDD reported some motivational deficits as measured by a subset of items on the HAM-D, and in fact these deficits predicted just over half the variance in global life functioning (Fervaha et al., 2016). Abilities in social cognition (in this case, comprehending confusing communication and integrating ideas about the self and others) and metacognition (described as the ability to hold multiple world perspectives) improved in remission relative to active illness, but not to a level equivalent with HCs (Ladegaard et al., 2016). Together, these studies show that after treatment or remission from active MDD, many individuals still experience residual deficits in executive function, motivational, and social cognitive functioning. Participants in the present study exhibited reduced hedonic functioning on self-reports, despite being remitted/euthymic, but not on

objective behavioral performance measures of reward functioning. It may be that although many cognitive functions are influenced by residual mood symptoms, reward functioning is largely unaffected. Of course, with all these examples of residual deficits during remission, it is very difficult to disentangle state effects, trait factors, and scars of illness.

4.2 **Brain Activation During Reward Anticipation**

There were few group differences in neural activation during the anticipation of a possible reward, with the HC group showing hyperactivation in the right declive relative to the HMD group. Previous work has found the declive to be involved in motor and counting tasks (Wu et al., 2013) and working memory and inhibitory control (Niendam et al., 2012). In a study of participants with an obesity-associated risk allele, decreasing BMI was associated with increasing neural activity in the declive during a task requiring participants to discriminate between high- and low-calorie foods (Wiemerslage et al., 2015). Cerebellar activation has also been associated with viewing pictures that elicited disgust and happiness (Schienle & Scharmuller, 2013). Activation of the cerebellum during reward anticipation may reflect the working memory and cognitive control needed to perform the MIDT well, as well as the affective content of the task. Dichter and colleagues (2012) reported increased activation in the right cerebellum in rMDD compared to HC participants, which, although opposite to the direction of activation observed in our data, suggests a role for the right cerebellum in reward anticipation. Our results contrast the finding reported by Dichter and colleagues (2012) that activation in the bilateral anterior cingulate and right midfrontal gyrus was increased in rMDD participants relative to HCs during reward anticipation. The disparity in our findings and those reported by Dichter and colleagues (2012) could be explained by our sample including individuals with subthreshold presentations (according to DSM-5 and in line with RDoC). We

found no group differences in VS activation during the MIDT, which is in line with a previous study in which NAcc activation failed to distinguish MDD and HC groups during reward anticipation in the MIDT (Knutson et al., 2008). The aberrant reward circuit activation typically seen in active MDD and BP patients may have normalized in the remitted state, relative to HCs, which would suggest a lack of a reward-related neural signature in mood disorders that would be a trait or scar of illness (Peters et al., 2017).

4.3 **Connectivity from the Reward Network to the SEN and DMN**

The overall trend in our connectivity results was that, in HMD relative to HC, the reward nodes showed a mean increased connectivity to the SEN and decreased connectivity to the DMN. Reward-SEN connectivity was slightly higher in HMD compared to HC, which, although not statistically significant, was directionally consistent with our hypothesis. The difference may have not reached significance because our participants were not in the active phase of illness, whereas the literature mainly describes SEN connectivity in actively depressed individuals. We found no differences in reward-DMN connectivity between HMD and HC groups. These findings contrast with a meta-analysis reporting hypoconnectivity between the affective network and DMN and hyperconnectivity within the DMN and in MDD (Kaiser et al., 2015), although the networks and comparisons in that meta-analysis were not directly comparable to those in the present study.

Interestingly, the amygdala and dACC emerged as regions with either relatively increased or decreased connectivity to the networks of interest. In HMD compared to HC, the dACC had less connectivity with both the DMN and SEN, whereas the amygdala showed less connectivity to the DMN but greater connectivity to the SEN. Connectivity between the dACC and SEN has previously been found to be relatively decreased in depressed adolescents (Pannekoek et al.,

2014). The dACC is thought to be involved in error monitoring particularly in affective contexts, and indeed previous studies have found dACC hyperactivation during reward anticipation (Smoski et al., 2009). Decreased connectivity between the dACC and SEN could signify a vulnerability or consequence of illness.

Previous work has revealed reduced rsFC between the amygdala and regions that encompass part of the DMN (dorsomedial PFC and fronto-insular operculum) in individuals with MDD relative to HCs, suggesting that lessened connectivity between affective/salience and default mode regions may be a biomarker of depression (Tahmasian et al., 2013). Reduced connectivity between the amygdala and PCC has been observed in women with post-partum depression, compared to healthy post-partum women (Chase et al., 2013). Some researchers have theorized that the amygdala, by providing information to the medial thalamus, may contribute to a corticothalamic pathway relating to DMN hyperconnectivity and rumination in MDD (Hamilton et al., 2015).

In the HMD group compared to HC, overall the reward circuit showed hyperconnectivity with the SEN, although it was not a significant difference. It should be noted that the reward and salience-emotion networks as we defined them overlap in the amygdala, which unsurprisingly showed very strong connections to the SEN in our analyses. One takeaway is that the reward network and SEN are highly related both functionally and anatomically. In monkeys choosing between differently rewarded stimuli, amygdala lesions reduced the amount of neurons in the OFC that were coding for reward quantity (Rudebeck et al., 2013), suggesting that the amygdala has an important role in the neural representation of reward. The amygdala is more recently considered to be part of the core reward circuit (Heshmati & Russo, 2015).

Contrary to our hypothesis, we did not observe differences in network homogeneity between groups. There is evidence that functional connectivity differs based on level of residual symptoms of depression (Delaveau et al., 2017), or active versus remitted state (Jacobs et al., 2016), so the contrast between our findings and those in the literature could be due to the remitted status of our participants with mood disorders. It is also important to note that we evaluated connectivity between the reward network and SEN or DMN, not purely within-SEN or within-DMN connectivity.

RsFC may reflect a trait-like organization of the brain, which then may be further susceptible to the effects of psychiatric disease. Previous work has found a strong relationship between functional and structural connectivity, with rsFC tending to be highly correlated with white matter integrity (Van Den Heuvel & Pol, 2010) and structurally connected areas of the cortex having higher rsFC than regions without structural connections (Honey et al., 2009).

Task-based fMRI, in contrast to rsFC, may be more sensitive to active symptoms and state factors of illness. Several studies reported that pre-treatment BOLD signal in limbic and prefrontal regions predicted desirable post-treatment outcomes in OCD, depression, and anxiety disorders (Linden, 2006; Forbes et al., 2010; Langenecker et al., 2018). Linden (2006) reviewed studies of OCD, PTSD, and depression in which symptom provocation was followed by BOLD signal changes in brain areas relevant to each disease. However, another study failed to show a correlation between pre-treatment BOLD signal (in the subgenual ACC) and post-treatment depressive symptoms (Siegle et al., 2012) and other studies have observed changes in rsFC related to symptom induction or psychotherapy response (Linden, 2006). These findings suggest that activation during fMRI tasks may reflect the current symptom state, although there is no consensus in the literature.

4.4 Trait Reward-Responsiveness and Mood Symptom Fluctuation

Contrary to our hypothesis, we found no moderating effect of baseline reward-responsiveness on depressive symptoms over time, across groups or in HMD group separately. This null finding was in contrast to a previous study which found that BAS-RR scores at baseline predicted depression scores at eight-month follow-up (Kasch et al., 2002). However, the study by Kasch and colleagues recruited actively depressed participants, who had slightly lower BAS-RR scores at baseline than the HMD participants in the current study. In the present sample, HMD and HC groups had very similar BAS-RR scores. It could be that BAS-RR is a predictor of depressive symptoms in active but not remitted MDD. In support of this idea is a previous study that found that BAS-RR did not significantly predict time to a major depressive episode onset in bipolar spectrum participants (Alloy et al., 2008). In a cross-sectional study of adolescents with bipolar I, II, or not otherwise specified, BAS-RR failed to significantly predict current depression symptomology whereas it negatively correlated with motoric mania symptoms; the authors noted that both these findings were inconsistent with previous literature (Biuckians et al., 2007). BDI scores in the HMD group were also quite stable over time, indicating that individuals with remitted mood disorders do not experience much variability in their depression symptoms during naturalistic follow-up.

Baseline reward-responsiveness did not predict mania symptoms over time, either across groups or in HMD group separately. This null finding somewhat contrasted a study reporting that higher BAS-RR predicted shorter time to bipolar spectrum participants' first episode of hypomania or mania (Alloy et al., 2008). Higher reward-responsiveness may be related to the onset of a first episode but not to episodes later in the course of illness. Another previous study reported no correlation between BAS-RR and lifetime manic symptoms, although this study was

limited by its analog sample of undergraduates and the fact that they did not measure current manic symptoms (Fulford, Johnson, & Carver, 2008).

Although BAS-RR alone did not predict the course of manic symptoms over the follow-up period, a three-way interaction emerged between group, BAS-RR, and time in predicting mania scores. The mania scores of participants with higher baseline BAS-RR remained more stable over time, while the mania scores of participants with lower BAS-RR increased over time. This finding is inconsistent with the previous study by Alloy and colleagues (2008) in which individuals with higher BAS-RR went on to develop hypomanic/manic episodes more quickly than those with lower BAS-RR. Our data suggest that BAS-RR may be a factor in symptom variability over the course of illness, although we do not yet know whether it would be a vulnerability or a consequence of illness. Our mixture of rMDD and eBP (with the latter group being relatively small) may have confounded relationships between mania symptoms, depression symptoms, and BAS-RR. In another study of participants with bipolar I and II, BAS-RR was positively associated with hypomanic and manic symptom variability in individuals with bipolar I, although BAS-RR did not predict depressive or hypomanic/manic episodes at a six-month follow-up (Fletcher, Parker, & Manicavasagar, 2013). It should be noted that, in the present study, mania scores in both groups were fairly low and there was little variance in mania symptoms, so our findings can only hint at a potential clinical utility. A longitudinal study of individuals with active mood symptoms, and changes from active to remitted phases, would provide a clearer answer as to whether self-reported reward-responsiveness moderates the naturalistic course of mania symptoms.

4.5 No Relationship Between Reward Task Performance and Symptom Changes

We did not obtain results that supported our hypothesis that better performance on objective measures of reward function would serve as essentially a protective factor for individuals with a history of mood disturbance in keeping depression symptoms low over time. There was no evidence of a cross-lagged relationship between amount of money won on the MIDT and depression scores. Depressive symptoms in the HMD group were more stable than expected and the group mean scores remained in the minimal to low-mild range. Self-reported depressive symptoms at Times 1 and 2 predicted depression scores at the subsequent assessments. Amount of money won at the mid-point of the study predicted amount won at the final assessment. This is the first study to our knowledge to examine the value of objective metrics of reward anticipation in predicting depression symptoms over time. Some individuals with mood disorders have a more primarily anhedonic type of depressive episode, and in these individuals perhaps objective reward task performance would serve as a good predictor of depressive symptoms. Residual depressive symptoms did appear to be good predictors of future symptoms and MIDT performance predicted future MIDT performance.

4.6 **Limitations**

Limitations of the current study include using a clinician-administered measure to assess mania symptoms but a self-report measure to assess depressive symptoms, relatively small sample sizes at Time 2 and Time 3, unequal numbers of participants with rMDD versus eBP in the HMD group, limited range of YMRS scores, and varying length of time between study visits. Restricted range of YMRS scores could be partially reflective of participants with BP having difficulty recognizing manic symptoms in themselves, due to decreased insight. Future similar projects should aim for larger sample sizes, which might enhance the ability to detect moderator and mediator effects of reward measures. Longer follow-up periods would allow time for more

variability in symptoms over time, particularly hypomanic/manic symptoms, and enable greater precision in modeling the naturalistic course of illness. Future studies could utilize ecological momentary assessment to capture a more granular picture of mood symptom fluctuation, which may potentially enable more accurate prediction by affective measures like BAS-RR and the MIDT. Future research could oversample for individuals with predominantly anhedonic, amotivated presentations of MDD, as the MIDT may be more sensitive in eliciting performance and BOLD response differences in that group of individuals.

4.7 **Conclusions**

In sum, the current study aimed to elucidate cross-sectional and longitudinal differences in reward functioning between individuals with a history of MDD or BP and healthy comparisons. Self-reported affect and anhedonia differentiated the HMD and HC groups, whereas objective measurements of reward failed to differentiate groups or to predict naturalistic symptom fluctuation. We observed increased resting-state connectivity between reward and salience regions and decreased connectivity between reward and default mode regions. Our hypotheses regarding moderators and mediators were not supported. This study was the first to examine objective reward performance as a potential mediator of symptom fluctuation in individuals with past mood disturbance, and in combination with the lack of behavioral performance differences on the reward task, we found limited evidence of the MIDT's clinical relevance to individuals not in the active phase of mood disorder, although it revealed interesting neural activation differences. Resting-state connectivity allowed us to observe interesting relationships between networks and groups. Considering the existing literature, rsFC may be more sensitive to trait biomarkers of disease, relative to behavioral performance and task-based fMRI findings.

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Table I. *Elements of the RDoC Positive Valence System Included in the Present Study*

Construct	Subconstruct	Brain	Self-Report	Paradigms
Approach Motivation	Reward Valuation		BAS-RR	
	Effort Valuation / Willingness to Work	VS		
	Expectancy / Reward Prediction Error	VS, SEN	TEPS Anticipatory Scale	
Initial Responsiveness to Reward Attainment		VS, SEN	TEPS Consummatory Scale, PANAS	MIDT
Sustained/Longer-Term Responsiveness to Reward Attainment		VS, SEN, DMN	BAS-RR	MIDT
Reward Learning		SEN		

VS, ventral striatum; SEN, salience and emotion network; DMN, default mode network; BAS-RR, Behavioral Activation Scale-Reward Responsiveness; TEPS, Temporal Experience of Pleasure Scale; PANAS, Positive and Negative Affect Scale; MIDT, Monetary Incentive Delay Task.

Table II. *Demographics and Clinical Characteristics at Diagnostic Interview*

	HC	HMD			All
	<i>n</i> = 43	<i>n</i> = 132	<i>t</i> / <i>X</i> ²	<i>p</i>	<i>n</i> = 175
Age	22.53 (3.09)	23.33 (3.48)	-1.33	ns	23.13 (3.40)
% Female	58%	70%	1.96	ns	67%
Education	14.93 (1.83)	14.89 (2.02)	.10	ns	14.90 (1.97)
Race			19.37	<.001	
African American/Black	5 (11.6%)	26 (19.7%)			31 (17.7%)
Asian	14 (32.5%)	9 (6.8%)			23 (13.1%)
Caucasian/White	19 (44.2%)	81 (61.4%)			100 (57.1%)
More than one	3 (7%)	8 (6.1%)			11 (6.3%)
Unknown	2 (4.7%)	8 (6.1%)			10 (5.7%)
Ethnicity			.12	ns	
Hispanic	5 (11.6%)	18 (13.6%)			23 (13.1%)
Not Hispanic	38 (88.4%)	114 (86.4%)			152 (86.9%)
Estimated IQ	106.43 (7.74)	107.35 (9.89)	-.54	ns	107.12 (9.39)
Ham-D	.50 (.86)	4.03 (4.20)	-8.83	<.001	
Ham-A	1.05 (1.34)	5.13 (5.22)	-8.08	<.001	
BAI	2.74 (3.58)	13.16 (11.23)	-9.28	<.001	

HC, healthy control; HMD, history of mood disorder; Ham-D, Hamilton Depression Rating Scale (17-item); Ham-A, Hamilton Anxiety Rating Scale; BAI, Beck Anxiety Inventory; BAS-RR, Behavioral Activation Scale Reward Responsiveness.

Table III. *Self-Report and Behavioral Measures of Reward Function*

	HC	HMD	<i>t</i>	<i>p</i>
PANAS – state positive, time 1	31.99 (8.41)	27.91 (8.02)	2.56	.01
PANAS – state negative, time 1	11.81 (3.00)	17.63 (6.67)	-5.09	<.01
BAS-RR, time 1	17.64 (1.77)	16.89 (2.73)	2.09	.04
SHAPS, time 1	48.33 (6.38)	44.58 (6.80)	2.65	.01
SHAPS, time 3	52.15 (3.83)	45.39 (7.28)	4.09	<.01
TEPS – anticipatory, time 3	47.00 (8.36)	43.88 (6.15)	1.40	.17
TEPS – consummatory, time 3	38.85 (5.51)	34.91 (6.06)	2.03	.048
AMW time 1, in scanner	19.21 (18.33)	24.56 (16.43)	-1.60	.11
Win trial accuracy	.71 (.12)	.71 (.15)	.03	.98
Loss trial accuracy	.62 (.19)	.67 (.17)	-1.43	.16
Neutral trial accuracy	.51 (.20)	.54 (.22)	-.01	.99
Win trial reaction time in run 4	230.60 (23.78)	234.29 (31.11)	-.61	.54
Neutral trial reaction time in run 4	229.32 (44.49)	231.32 (36.20)	-1.12	.27
AMW time 1, outside scanner^	41.76 (9.36)	39.69 (10.74)	1.12	.26
Win trial accuracy	.86 (.09)	.85 (.11)	.48	.63
Loss trial accuracy	.87 (.10)	.86 (.13)	.47	.64
Neutral trial accuracy	.78 (.16)	.78 (.14)	.17	.86
AMW time 2, outside scanner	43.76 (5.89)	40.98 (11.10)	.98	.33
AMW time 3, outside scanner	41.83 (7.75)	40.26 (9.68)	.52	.61

HC, healthy control; HMD, history of mood disorder; PANAS, Positive and Negative Affect Scale; BAS-RR, Behavioral Activation System Reward Responsiveness; SHAPS, Snaith Hamilton Pleasure Scale; TEPS, Temporal Experience of Pleasure Scale; AMW, Amount of money won on the titrated Monetary Incentive Delay Task.

^ Completed during the neuropsychological evaluation, which was prior to fMRI at Time 1.

Table IV. *Comparison of Remitted MDD and Euthymic BP Participants on Variables of Interest in Aims 1 and 2*

	rMDD	eBP	<i>t</i>	<i>p</i>
SHAPS, time 1	44.99 (6.69)	42.88 (7.18)	1.15	.25
SHAPS, time 3	44.43 (7.33)	50.80 (4.32)	-1.87	.07
TEPS – consummatory, time 3	34.43 (5.80)	37.60 (7.50)	-1.08	.29
PANAS – state positive, time 1	27.36 (7.99)	29.95 (8.02)	-1.25	.21
PANAS – state negative, time 1	17.86 (7.01)	16.79 (5.32)	.62	.54
BAS-RR, time 1	16.83 (2.62)	17.11 (3.15)	-.47	.64
BDI, time 1	11.05 (10.44)	10.04 (8.79)	.47	.64
BDI, time 2	12.35 (10.45)	11.13 (6.53)	.32	.75
BDI, time 3	15.71 (12.73)	9.00 (6.52)	1.78*	.10
YMRS, time 1	1.82 (2.30)	3.41 (5.55)	-1.46*	.16
YMRS, time 2	2.07 (2.29)	2.25 (1.55)	-.25	.80
YMRS, time 3	2.11 (2.08)	2.40 (2.61)	-.28	.78

*Equal variances not assumed.

SHAPS, Snaith Hamilton Pleasure Scale; TEPS, Temporal Experience of Pleasure Scale; PANAS, Positive and Negative Affect Scale; BAS-RR, Behavioral Activation System Reward Responsiveness; BDI, Beck Depression Inventory II; YMRS, Young Mania Rating Scale.

Table V. *Clusters of Significant Activation During Target Anticipation in Win Trials Compared to Neutral Trials, $p < .01$*

Contrast	Region	BA	MNI coordinates ^a			Z	mm ³
			x	y	z		
HC > HMD	Declive (posterior cerebellum)	-	24	-66	-18	3.40	984
W-N across groups	Precentral gyrus, postcentral gyrus, supplementary motor area, parietal inferior lobule, supramarginal gyrus, cingulate, caudate, pallidum, putamen, insula, thalamus, parahippocampal gyrus, hippocampus, superior and inferior temporal gyri, frontal gyri	6, 24, 3, 4, 40, 13, 32, 31, 2	-30	-26	50	6.70	169,960
	Anterior and posterior cerebellum	-	-30	-26	62	6.70	
	Lingual gyrus	30	2	-60	-36	6.60	
	Calcarine sulcus	30	-24	-60	2	3.66	976
	Supramarginal gyrus	40	22	-70	4	3.00	600
	Precentral gyrus	4	42	-36	22	3.50	2392
			20	-26	54	3.95	1120

HMD, history of mood disorder; HC, healthy control; W-N, win minus neutral; BA, Brodmann area

^a x, y, z = MNI (Montreal Neurological Institute) coordinates

Table VI. *Group Differences in Connectivity from Reward Circuit Regions* to SEN and DMN*

	HC n = 29	HMD n = 78	<i>t</i>	<i>p</i>
Connectivity to DMN				
Left reward regions	.12 (.05)	.11 (.05)	1.02	.31
Right reward regions	.12 (.04)	.11 (.05)	1.75	.08
All bilateral reward regions	.12 (.04)	.11 (.04)	1.52	.13
VSs	.13 (.08)	.12 (.07)	.37	.71
VS _i	.13 (.08)	.12 (.07)	.21	.83
DLPFC	.05 (.05)	.06 (.07)	-.57	.57
Amygdala	.21 (.08)	.17 (.08)	2.00	.048
dACC	.11 (.09)	.07 (.08)	2.06	.04
Connectivity to SEN				
Left reward regions	.18 (.06)	.16 (.05)	1.50	.14
Right reward regions	.13 (.04)	.15 (.05)	-2.60	.01
All bilateral reward regions	.15 (.05)	.16 (.05)	-.51	.61
VSs	.21 (.06)	.20 (.07)	.74	.46
VS _i	.28 (.09)	.28 (.08)	.40	.69
DLPFC	.03 (.05)	.02 (.07)	1.04	.30
Amygdala	.18 (.06)	.28 (.08)	-6.39	<.001
dACC	.06 (.07)	.02 (.07)	2.77	.01

* VSs (superior ventral striatum), VS_i (inferior ventral striatum), DLPFC (dorsolateral prefrontal cortex), amygdala, dACC (dorsal anterior cingulate cortex).

HC, healthy control; HMD, history of mood disorder; DMN, default mode network; SEN, salience and emotion network.

Table VII. *Depression and Mania Symptoms Over Time*

	HC	HMD	<i>t</i>	<i>p</i>
BDI, 1	1.43 (2.12)	11.12 (10.24)	-8.49*	<.001
BDI, 2	1.41 (2.18)	12.15 (9.85)	-7.07*	< .001
BDI, 3	1.62 (2.81)	14.70 (12.17)	-5.80*	<.001
YMRS, 1	.36 (.96)	2.08 (3.30)	-5.17*	<.001
YMRS, 2	.17 (.58)	2.11 (2.13)	-6.14*	<.001
YMRS, 3	.31 (1.11)	2.15 (2.12)	-3.83	<.001

*Equal variances not assumed.

HC, healthy control; HMD, history of mood disorder; BDI, Beck Depression Inventory II; YMRS, Young Mania Rating Scale.

Table VIII. *Modeling Depression and Mania Symptoms Over Time*

Parameter	Model 1 (HC and HMD)						Model 2 (HMD only)					
	Depression (BDI)			Mania (YMRS)			Depression (BDI)			Mania (YMRS)		
	Est.	SE	<i>p</i>	Est.	SE	<i>p</i>	Est.	SE	<i>p</i>	Est.	SE	<i>p</i>
Intercept	-.07	.06	.27	-.10	.06	.09	-.07	.06	.26	-.10	.06	.09
Time	.00	.0001	.62	.0001	.0001	.58	.00	.00	.61	.0001	.0001	.57
BAS-RR	.03	.05	.54	.01	.06	.85	.03	.05	.54	.01	.06	.84
BAS-RR * Time	.00	.00	.74	.00	.0001	.81	.00	.00	.76	.00	.0001	.81
Group	-.79	.10	<.0001	-.44	.06	<.0001						
Group * Time	-.0001	.0002	.61	.00	.0001	.89						
Group * BAS-RR	-.09	.11	.39	-.08	.06	.23						
Group * Time * BAS-RR	.0003	.0001	.06	.0004	.0001	.002						

HC, healthy control; HMD, history of mood disorder; BAS-RR, Behavioral Activation System Reward Responsiveness; BDI, Beck Depression Inventory II; YMRS, Young Mania Rating Scale.

Table IX. *Path Analysis of Depression Symptoms and Amount of Money Won Over Time (HMD Only)*

	Path		Estimate	Standard Error	<i>t</i>
AMW 1	==>	BDI 2	.13	.11	1.28
AMW 2	==>	BDI 3	.02	.12	.19
BDI 1	==>	AMW 2	.13	.17	.72
BDI 2	==>	AMW 3	-.12	.13	-.87
BDI 1	==>	BDI 2	.81	.06	12.68*
BDI 2	==>	BDI 3	.72	.09	8.28*
AMW 1	==>	AMW 2	.14	.17	.82
AMW 2	==>	AMW 3	.65	.10	6.30*
AMW 2	<==>	BDI 2	-.04	.10	-.35
AMW 3	<==>	BDI 3	-.16	.09	-1.74

HMD, history of mood disorder; BDI, Beck Depression Inventory II; AMW, amount of money won. Time points indicated by 1, 2, 3.

* $p < .05$

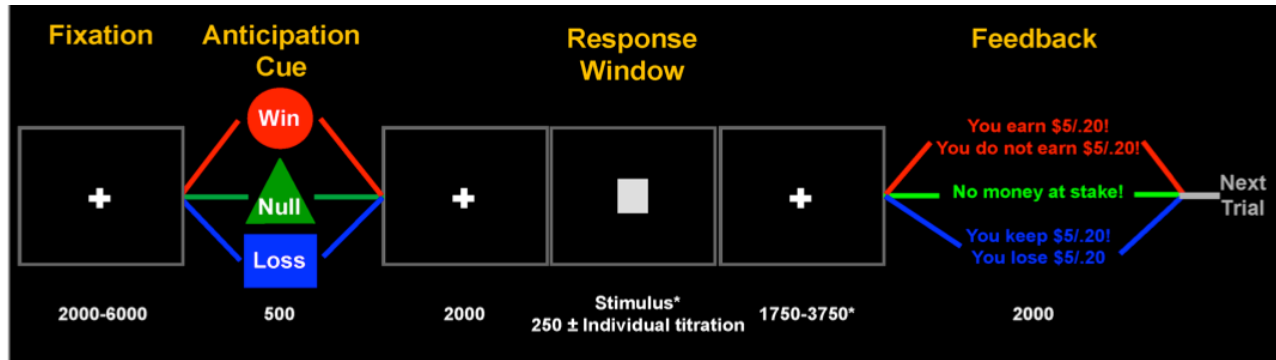


Figure 1. Monetary incentive delay task design (previously published in DelDonno et al., 2015).

A fixation cross was presented, followed by a cue indicating the type of upcoming trial. The fixation cross returned, followed by the response window individualized in length per each participant's baseline reaction time. Then after a jittered delay, participants received feedback on the outcome of the trial.

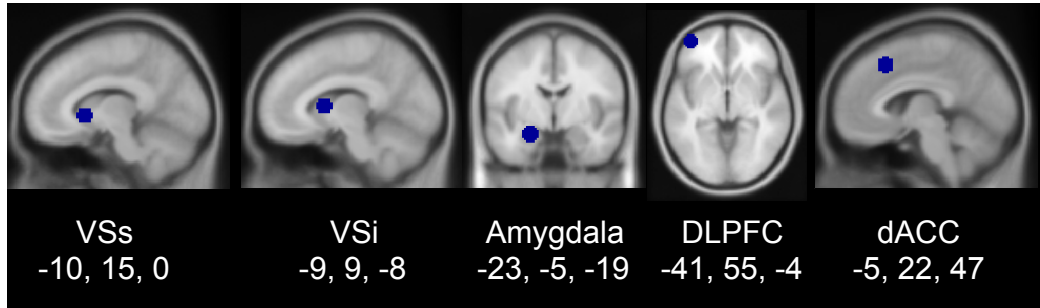


Figure 2. Reward circuit seeds (left side displayed). The superior and inferior ventral striatum, amygdala, dorsolateral prefrontal cortex, and dorsal anterior cingulate were used as seeds in connectivity analyses.

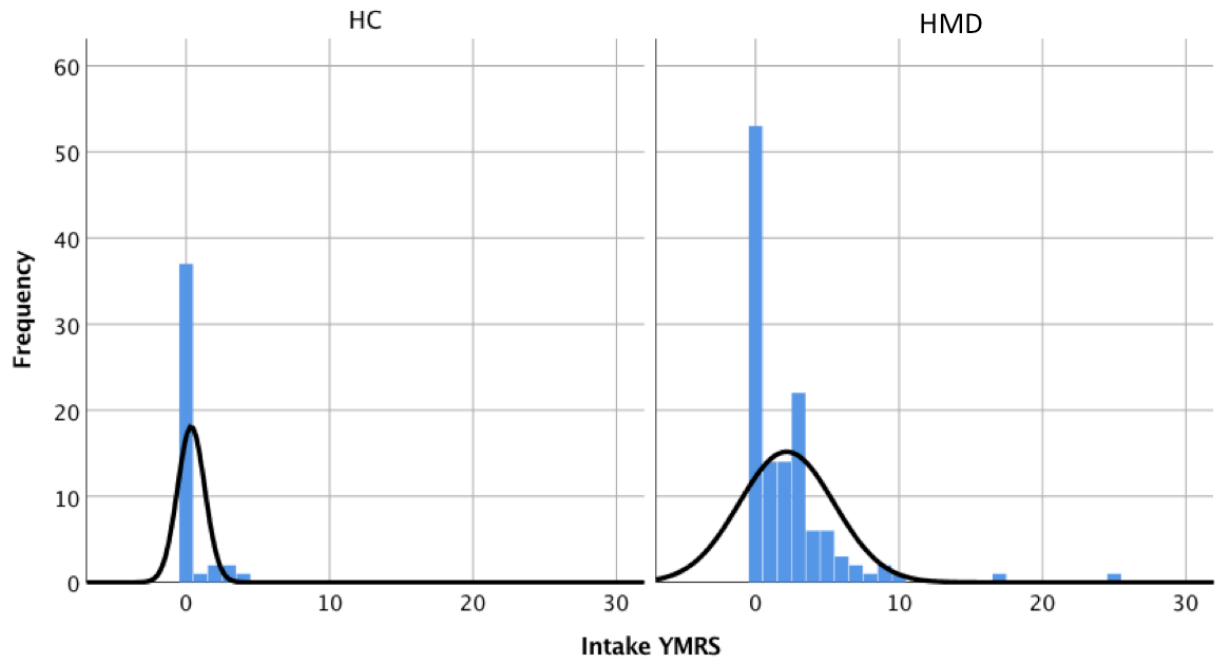


Figure 3. Distribution of Young Mania Rating Scale scores at Time 1. The distribution retained the same shape at the second and third assessments.

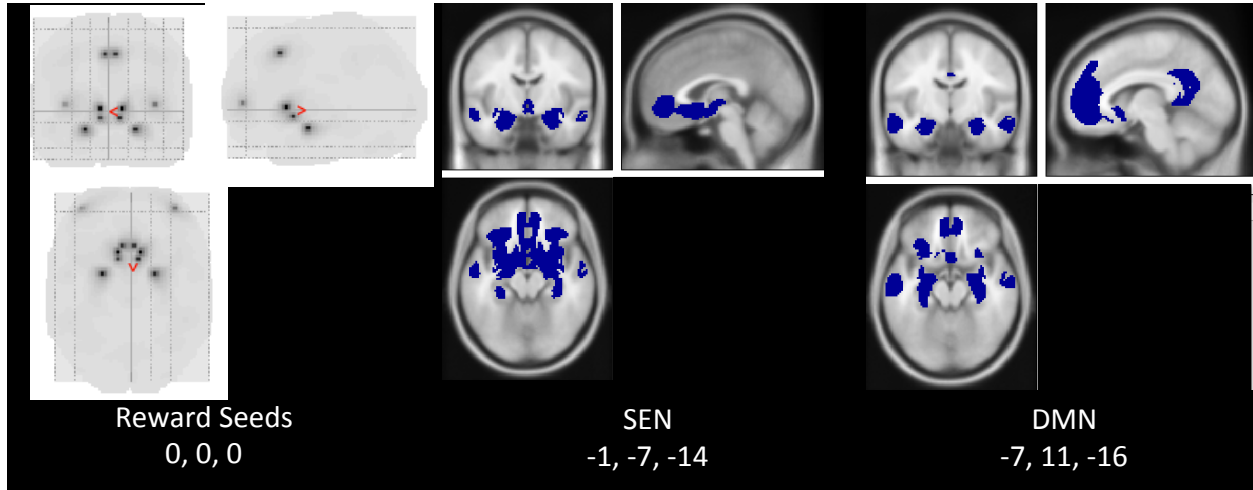


Figure 4. Reward network ROIs (superior ventral striatum, inferior ventral striatum, dorsolateral prefrontal cortex, amygdala, and dorsal anterior cingulate cortex), salience and emotion network (SEN) mask, and default mode network (DMN) mask.

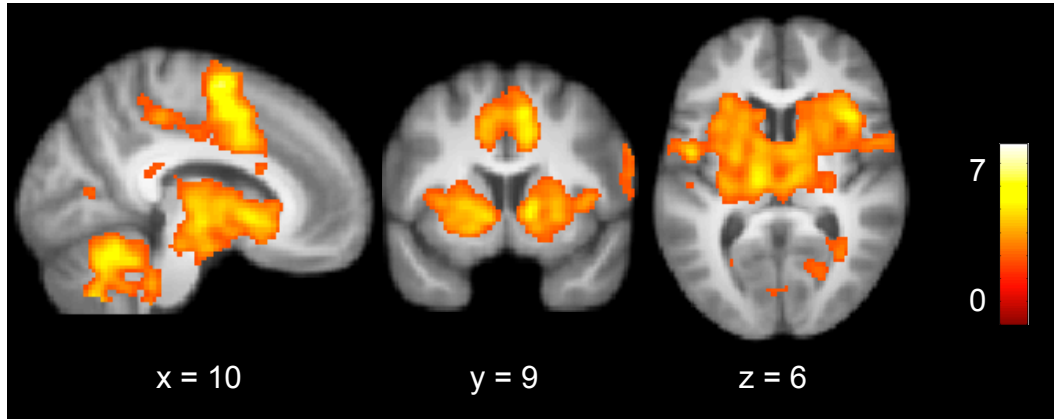


Figure 5. Whole-brain activation during anticipation of win trials compared to neutral trials in the MIDT. Activation was observed in the VS, dACC, DLPFC, right anterior superior insula, and other subcortical reward circuit regions.

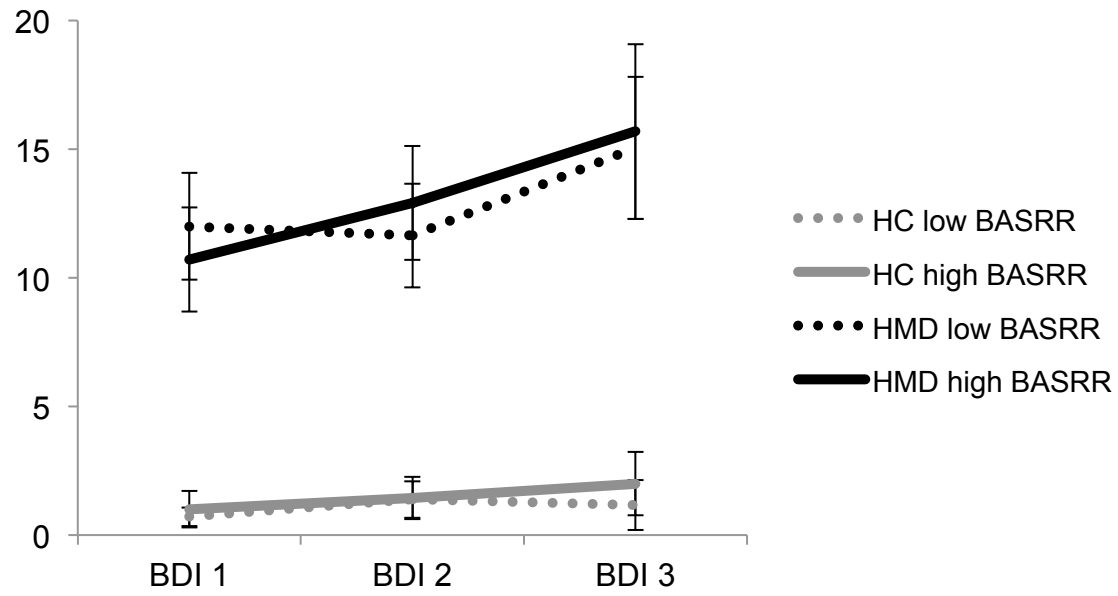


Figure 6. Group predicted depression scores (BDI) across the follow-up period, whereas baseline self-reported trait reward-responsiveness (BASRR) did not.

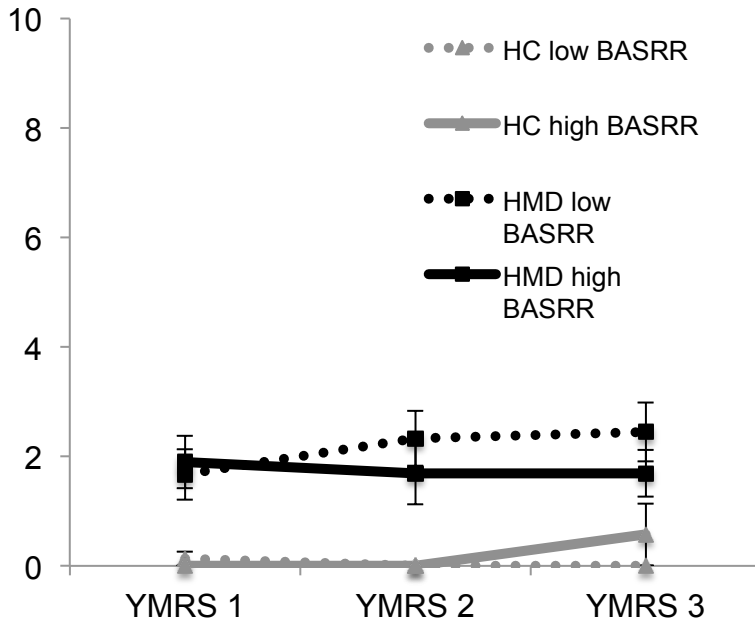


Figure 7. The interaction of group, baseline reward-responsiveness (BASRR), and time predicted mania scores (YMRS). BASRR is shown here as a median split, although in analyses was treated as a dimensional variable.

APPENDIX

UNIVERSITY OF ILLINOIS AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Approval Notice Amendment to Research Protocol and/or Consent Document – Expedited Review UIC Amendment # 13

May 17, 2017

Scott Langenecker, Ph.D
Psychiatry
1601 W. Taylor St
Psychiatry, M/C 912
Chicago, IL 60612
Phone: (312) 996-0085 / Fax: (312) 996-7658

**RE: Protocol # 2013-0828
“Dimensional RDoc Modeling across the Range of Negative Mood Dysfunction
(MNMS)”**

Dear Dr. Langenecker:

Members of Institutional Review Board (IRB) #3 have reviewed this amendment to your research and/or consent form under expedited procedures for minor changes to previously approved research allowed by Federal regulations [45 CFR 46.110(b)(2) and/or 21 CFR 56.110(b)(2)]. The amendment to your research was determined to be acceptable and may now be implemented.

Please note the following information about your approved amendment:

Amendment Approval Date: May 11, 2017

Amendment:

Summary: UIC Amendment #13, received April 10, 2017, involves the following changes:

1. Change in research personnel with the addition of John Bark; change in research role of Dr. Lisaanne Jenkins to Co-Investigator; and the removal of Erica Hymen, Alyssa Barba, Osvaldo Romero and Sherjeel Hassan.
2. The most recent Data Safety Monitoring Board meeting minutes from the February 8, 2017 meeting have been provided.
3. The Brain Behavior Research foundation (KC#086212) through the National Alliance for

Research on Schizophrenia and Depression (NARSAD) award has been added as a new funding source. New funding for a NARSAD award allows the researchers to ask participants to return for more extensive scanning, in particular, diffusion tensor imaging of white matter.

Itemized changes to the research documents include:

- a) Dr. Jenkins added to Co-Investigators (pg 1)
- b) New funding source added to Sponsor (pg 1)
- c) Description of additional visits (pg 19). Visits 5 and 6 are identical to visits 3 and 4, and are included so that the researchers can compare the same data collected from participants across two timepoints. Visit 7 is a new additional testing visit that is being added due to new funding becoming available. Visit 7 is comprised of two components: additional neuropsychological testing (described on pgs 19-20) and a brain scan (Human Connectome visit, described on pg 21). The additional neuropsychological testing visit is called visit A within Visit 7. The Human Connectome is visit B within Visit 7. Some participants may qualify to participate in both Visit A and Visit B, which we are calling Visit C. In other words, participants choosing to participate in Visit 7 have three options for participating based upon their eligibility: Visit A, B, or C. Visit C is merely the combination of visits A and B.
- d) The document “MNMS Subject notification of opportunities for additional visits V1.1, 5/3/17” is the text of the email researchers will send to participants to invite them to participate in Visit 7. When participants provided consent, they consented to being re-contacted in the future. Participants will be re-contacted by email and so most will respond via email. However, a phone number is included so that participants can choose to respond by email or phone.
- e) The consent form has been revised to include more details about Visit 6 and to now describe the newly added Visit 7 (including the Human Connectome Visit) on page 3. On page 9 of the consent form, the researchers updated the compensation scheme to reflect the additional Visit 7 that participants may be compensated for.
- f) Changes to the Initial Review form include adding a source of funding (pg 3), adding a brief description of Visit 7 and the Human Connectome Visit (pgs 11-12), updating the total possible amount of compensation (pg 34), and updating details of the compensation scheme per visit (pg 35-36).

The consent (V.4, 3.17.17), research protocol (version 5, 3/15/17), Initial Review application (version 4, 3/16/17), Appendices P and Z and have been updated to reflect the proposed changes.

<u>Approved Subject Enrollment #:</u>	350
<u>Performance Sites:</u>	UIC
<u>Sponsor:</u>	NIMH, Brain & Behavior Research Foundation
<u>PAF#:</u>	00028770, 2016-05132

Grant/Contract No:

MH101487,KC # 086212

Grant/Contract Title:

Dimensional RDoc Modeling across the Range of Negative Mood Dysfunction (MNMS), Multimodal brain network predictors of recurrence in depression

Research Protocol(s):

- a) Dimensional RDoc Modeling Across the Range of Negative Mood Dysfunction (MNMS), Version 5, 3/15/17

Recruiting Material(s):

- a) MNMS Subject notification of opportunities for additional visits, V1.1, 5/3/17

Informed Consent(s):

- a) MNMS, V. 4, 3.17.17

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
04/10/2017	Amendment	Expedited	04/14/2017	Modifications Required
05/05/2017	Response To Modifications	Expedited	05/11/2017	Approved

Please be sure to:

→ **Use only the IRB-approved and stamped consent document(s) and/or HIPAA Authorization form(s) enclosed with this letter when enrolling subjects.**

→ Use your research protocol number (2013-0828) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure,

"UIC Investigator Responsibilities, Protection of Human Research Subjects"

(<http://tiger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf>)

Please note that the UIC IRB #3 has the right to ask further questions, seek additional information, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact the OPRS at (312) 996-1711 or me at (312) 355-1404. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Sheilah R. Graham, MPH
IRB Coordinator, IRB # 3
Office for the Protection of Research Subjects

Enclosure(s):

1. Informed Consent Document(s):

a) MNMS, V. 4, 3.17.17

2. Recruiting Material(s):

a) MNMS Subject notification of opportunities for additional visits, V1.1, 5/3/17

cc: Anand Kumar, Psychiatry, M/C 912

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CURRICULUM VITA

Sophie R. DelDonno, M.A.

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Education

Doctor of Philosophy Clinical Psychology University of Illinois at Chicago, Chicago, IL Dissertation: A Longitudinal Multimodal Study of Reward Functioning and Symptom Fluctuation in Mood Disorders	2019
Master of Arts Psychology University of Illinois at Chicago, Chicago, IL Thesis: Affective Predictors of Disrupted Reward-Seeking in Depression	2015
Bachelor of Arts , summa cum laude Psychology Stony Brook University, Stony Brook, NY	2011

Honors and Awards

Chancellor's Graduate Research Award, University of Illinois at Chicago	2017
Travel Award, National Network of Depression Centers	2016
Top Poster Award Nomination, Society of Biological Psychiatry	2016
Travel Award, University of Illinois at Chicago Psychology Department	2015, 2016
T32 Trainee in the Neuroscience of Mental Health	2015
Young Investigator Award, National Network of Depression Centers	2014
Honors Program in Psychology, Stony Brook University	2010 – 2011
Academic Achievement Award, Stony Brook University	2008 – 2011
Dean's List (all semesters), Stony Brook University	2007 – 2011
Provost's Out-of-State Scholarship, Stony Brook University	2007 – 2011

Current Position

Clinical Psychology Doctoral Intern

2018 – 2019

Department of Psychiatry & Behavioral Neuroscience, University of Chicago, Chicago IL

Training Director: Shona Vas, Ph.D.

- **Outpatient Services:** provide assessment, Cognitive Behavior Therapy (CBT) and other evidence-based psychotherapies to psychiatric outpatients with mood, anxiety, and substance use disorders
- **Severe Mental Illness and Obsessive-Compulsive and Related Disorders Clinic:** conduct intake assessments for and provide CBT to individuals with trichotillomania, OCD, and other severe mental illness
- **Women's Behavioral Health Service:** support girls and women regarding reproductive health decisions and collaborate with OB/GYN team for assessment and treatment planning; provide short-term CBT and interpersonal therapy for women with post-partum anxiety and depression, fertility issues, and pregnancy loss or termination
- **Eating Disorders Program:** conduct diagnostic assessments and provide CBT for Eating Disorders to adolescents and adults with anorexia nervosa, bulimia nervosa, binge eating disorder, and other feeding and eating disorders

Clinical Experience

Primary Care Behavioral Health Extern

2017 – 2018

Edward Hines Jr. VA Hospital, Hines, IL

Supervisor: Katherine Meyers, Ph.D.

- Conducted targeted psychological assessments for same-day referrals from primary care providers
- Provided brief psychotherapy to oncology and primary care patients
- Facilitated psychoeducational coping skills class for veterans with cancer
- Co-led therapy groups for patients with chronic pain using CBT and ACT

Psychology Extern

2016 – 2017

Addictive, Compulsive, and Impulsive Disorders Clinic

Department of Psychiatry & Behavioral Neuroscience, University of Chicago, Chicago, IL

Supervisor: Daniel Fridberg, Ph.D.

- Provided cognitive behavioral therapy and motivational interviewing to patients diverse in race, socioeconomic background, and sexual orientation with a range of mood, substance use, and impulsive disorders
- Facilitated individual and group smoking cessation therapy using the Courage To Quit program
- Conducted psychological evaluations of liver and kidney transplant candidates and presented findings to multidisciplinary transplant team

Graduate Level Therapist

2013 – 2017

Office of Applied Psychological Services

University of Illinois at Chicago, Chicago, IL

Supervisors: Amanda Lorenz, Ph.D., Nancy Dasso, Ph.D.

- Conducted intake interviews with clients seeking therapy or assessment
- Assessment practicum: Administered and scored neuropsychological assessment batteries and wrote integrated reports for clients presenting with a range of neurocognitive, neurodevelopmental, mood and anxiety, learning, or intellectual disorders
- Therapy practicum: Provided cognitive behavioral therapy or other appropriate evidence-based therapy (e.g. ACT, motivational interviewing) to clients diverse in age, race, sex, and socioeconomic background with a variety of presenting problems, including mood disorders, anxiety, substance use, personality disorders, amotivation, and interpersonal issues

Clinical Research Interviewer

2011 – 2013

McLean Hospital, Belmont, MA

Supervisor: Melissa Kaufman, M.D., Ph.D.

- Assessed current and past psychiatric history using the Mini International Neuropsychiatric Interview with community populations and mild traumatic brain injury research participants

Clinical Supervision Experience

Department of Psychiatry & Behavioral Neuroscience

2018 – 2019

University of Chicago, Chicago IL

- Supervise practicum student in providing CBT to adult outpatient with social anxiety and OCD; receive supervision of supervision from licensed clinical psychologist

Cognitive Neuroscience Center, Department of Psychiatry

2013-2018

University of Illinois at Chicago, Chicago IL

- Supervised junior graduate students conducting diagnostic interviews and symptom assessments for research participants with mood disorders
- Trained undergraduate research assistants in neuropsychological assessment of executive function, cognitive ability, and memory in research participants with late-life depression
- Mentored post-baccalaureate research assistants in data analysis and manuscript preparation

Publications

25. **DelDonno, S. R.**, Karstens, A., Cerny, B., Kling, L. R., Jenkins, L. M., Stange, J. P., Nusslock, R., Shankman, S., & Langenecker, S.A. The titrated monetary incentive delay task: Sensitivity, convergent and divergent validity, and neural correlates in an RDoC sample. (2019, in press). *Journal of Clinical and Experimental Neuropsychology*.
24. Patel, P. J., Dusane, S., **DelDonno, S. R.**, Langenecker, S. A., & Bhatt, T. (2018). Examining neural plasticity for slip-perturbation training – An fMRI study. *Frontiers in Neurology*, 9.
23. Stange, J. P., Jenkins, L. M., Bessette, K. L., Kling, L. R., Bark, J. S., Shepard, R., Hamlat, E. J., **DelDonno, S.**, Phan, K. L., Passarotti, A. M., Ajilore, O., & Langenecker, S. A. (2018). Predictors of attrition in longitudinal neuroimaging research: Inhibitory control, head movement, and resting-state functional connectivity. *Brain Connectivity*, 8(9), 527-536.
22. Langenecker, S. A., Jenkins, L. M., Stange, J. P., Chang, Y. S., **DelDonno, S. R.**, Bessette, K. L., Passarotti, A. M., Bhaumik, R., Ajilore, O., Jacobs, R.H. (2018). Cognitive control neuroimaging measures differentiate between those with and without future recurrence of depression. *NeuroImage: Clinical*, 20, 1001-1009.
21. Quinn, M. E., Stange, J. P., Jenkins, L. M., Corwin, S., **DelDonno, S. R.**, Bessette, K. L., Welsh, R.C., & Langenecker, S.A. (2018). Cognitive control and network disruption in remitted depression: a correlate of childhood adversity. *Social, Cognitive, and Affective Neuroscience*, 13(10), 1081-1090.
20. Bhatt, T., Patel, P., Dusane, S., **DelDonno, S. R.**, & Langenecker, S. A. (2018). Neural mechanisms involved in mental imagery of slip perturbation while walking: A preliminary fMRI study. *Frontiers in Behavioral Neuroscience*, 12.
19. Langenecker, S. A., Klumpp, H., Peters, A. T., Crane, N. A., **DelDonno, S. R.**, Bessette, K. L., Ajilore, O., Leow, A., Shankman, S. A., Walker, S. J., Ransom, M. T., Hsu, D. T., Phan, K. L., Zubieta, J-K., Mickey, B. J., Stange, J. P. (2018). Multidimensional imaging techniques for prediction of treatment response in major depressive disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*.
18. Bessette, K. L., Jenkins, L. M., Skerrett, K. A., Gowins, J. R., **DelDonno, S. R.**, Zubieta, J., McInnis, M. G., Jacobs, R. H., Ajilore, O., & Langenecker, S. A. (2018). Reliability, convergent validity and time invariance of default mode network deviations in early adult Major Depressive Disorder. *Frontiers in Psychiatry*, 9, 244.
17. Stange, J. P., Jenkins, L. M., Hamlat, E. J., Bessette, K. L., **DelDonno, S.**, Kling, L. R., Passarotti, A. M., Phan, K. L., Klumpp, H., Ryan, K. A., & Langenecker, S. A. (2018). Disrupted engagement of networks supporting hot and cold cognition in remitted major depressive disorder. *Journal of Affective Disorders*, 227, 183-191.
16. Jenkins, L. M., Skerrett, K., **DelDonno, S. R.**, Patron, V. G., Meyers, K. K., Peltier, S., Zubieta, J. K., Langenecker, S. A., & Starkman, M. N. (2018). Individuals with more severe depression fail to sustain nucleus accumbens activity to preferred music over time. *Psychiatry Research: Neuroimaging*, 275, 21-27.
15. **DelDonno, S. R.**, Jenkins, L. M., Crane, N. A., Nusslock, R., Ryan, K. A., Shankman, S. A., Phan, K. L., & Langenecker, S. A. (2017). Affective traits and history of depression are related to functional connectivity of the ventral striatum. *Journal of Affective Disorders*, 221, 72-80.

14. Jenkins, L. M., Barba, A., Stange, J. P., **DelDonno, S.**, Kling, L., Briceño, E., Weisenbach, S. L., Phan, K. L., Shankman, S., Welsh, R. C. and Langenecker, S. A. (2017). Integrated cross-network connectivity of amygdala, insula and subgenual cingulate associated with facial emotion perception in healthy controls and remitted major depressive disorder. *Cognitive, Affective, & Behavioral Neuroscience*, 17(6), 1242-1254.
13. **DelDonno, S. R.**, Weldon, A. L., Crane, N. A., Passarotti, A. M., Pruitt, P. J., Gabriel, L. B., Yau, W., Meyers, K. K., Hsu, D. T., Taylor, S. F., Heitzeg, M. M., Herbener, E., Shankman, S. A., Mickey, B. J., Zubieta, J. K., & Langenecker, S. A. (2015). Affective personality predictors of disrupted reward learning and pursuit in major depressive disorder. *Psychiatry Research*, 230(1), 56-64.
12. Langenecker, S. A., Crane, N. A., **DelDonno, S.**, Gabriel, L., Gowins, J., Nagel, C., Mickey, B., Zubieta, J. K., Mermelstein, R., & Martin, E. (2015). Adaptive reward learning is intact in young adults with remitted substance use and depressive disorders. *Drug & Alcohol Dependence*, 156, e121.
11. Webb, C. A., **DelDonno, S.**, & Killgore, W. D. (2014). The role of cognitive versus emotional intelligence in Iowa Gambling Task performance: What's emotion got to do with it?. *Intelligence*, 44, 112-119.
10. Dunning, J. P., **DelDonno, S.**, & Hajcak, G. (2013). The effects of contextual threat and anxiety on affective startle modulation. *Biological Psychology*, 94(1), 130-135.
9. Killgore W. D., Schwab Z. J., Kipman M., **DelDonno S. R.**, & Weber M. (2013). Insomnia-related complaints correlate with functional connectivity between sensory-motor regions. *Neuroreport*, 24(5), 233-240.
8. Killgore W. D., Schwab Z. J., Weber M., Kipman M., **DelDonno S. R.**, Weiner M. R., & Rauch S. L. (2013). Daytime sleepiness affects prefrontal regulation of food intake. *Neuroimage*, 71(1), 216-223.
7. Killgore, W. D. S., Schwab, Z. J., Tkachenko, O., Webb, C. A., **DelDonno, S. R.**, Kipman, M., Rauch, S. L., & Weber, M. (2013). Emotional intelligence correlates with functional responses to dynamic changes in facial trustworthiness. *Social Neuroscience*, 8(4), 334-346.
6. Killgore, W. D., Weber, M., Schwab, Z. J., Kipman, M., **DelDonno, S.**, Webb, C. A., & Rauch, S. L. (2013). Cortico-limbic responsiveness to high-calorie foods predicts weight status among women. *International Journal of Obesity*, 37, 1435-1442.
5. Webb, C. A., Schwab, Z. J., Weber, M., **DelDonno, S.**, Kipman, M., Weiner, M. R., & Killgore, W. D. (2013). Convergent and divergent validity of integrative versus mixed model measure of emotional intelligence. *Intelligence*, 41(3), 149-156.
4. Weber, M., Webb, C. A., **DelDonno, S. R.**, Kipman, M., Schwab, Z. J., Weiner, M. W., & Killgore, W. D. S. (2013). Habitual 'sleep credit' is associated with greater grey matter volume of the medial prefrontal cortex, higher emotional intelligence and better mental health. *Journal of Sleep Research*, 22(5), 527-534.
3. Killgore, W. D., Weber, M., Schwab, Z. J., **DelDonno, S. R.**, Kipman, M., Weiner, M. R., & Rauch, S. L. (2012). Grey matter correlates of trait and ability models of emotional intelligence. *Neuroreport*, 23, 551-555.
2. Killgore, W. D., Schwab, Z. J., Kipman, M., **DelDonno, S. R.**, & Weber, M. (2012). Voxel-based morphometric grey matter correlates of daytime sleepiness. *Neuroscience Letters*, 518(1), 10-13.

1. Kipman, M., Weber, M., Schwab, Z. J., **DelDonno, S. R.**, & Killgore, W. D. (2012). A funny thing happened on the way to the scanner: Humor detection correlates with gray matter volume. *Neuroreport*, 23, 1059-1064.

Manuscripts Under Review

1. **DelDonno, S. R.**, Mickey, B., Pruitt, P. J., Hsu, D. T., Weldon, A. L., Zubieta, J. K., & Langenecker, S. A. Influence of childhood adversity, approach motivation traits, and depression on neural substrates of reward.
2. Stange, J. P., Klumpp, H., Peters, A. T., Crane, N. A., **DelDonno, S. R.**, Bessette, K. L., Ajilore, O., Leow, A., Shankman, S. A., Hsu, D. T., Phan, K. L., Zubieta, J. K., Mickey, B. J., & Langenecker, S. A. Multidimensional imaging techniques for prediction of treatment response in major depressive disorder.
3. Stange, J. P., Jenkins, L. M., Pocius, S., Kreutzer, K., Bessette, K. L., **DelDonno, S. R.**, Kling, L. R., Bhaumik, R., Keilp, J. G., Phan, K. L. & Langenecker, S. A. Using resting state intrinsic network connectivity to identify suicide risk in mood disorders.
4. Kling, L. R., **DelDonno, S. R.**, Bessette, K. L., & Langenecker, S. A. Neuropsychological and functional connectivity profile of remitted depressed young adults at increased risk for manic episodes.

Conference Presentations

3. Trait reward-responsiveness and history of depression are related to ventral striatum connectivity. To be presented at the Association for Behavioral and Cognitive Therapies, Washington, D.C., November 15-18, 2018.
2. Reward-processing deficits in active but not remitted depression. Presented at the Annual National Network of Depression Centers Conference, Chicago, IL, October 24, 2014.
1. The impact of threat of shock on the defensive startle reflex. Presented at the Stony Brook Undergraduate Research and Creative Activities Conference, Stony Brook, NY, April 27, 2011.

Posters

34. **DelDonno, S.R.**, Mickey, B.J., Weldon, A.L., Pruitt, P.J., Jenkins, L.M., Skerrett, K.A., Kling, L., Zubieta, J.K., & Langenecker, S.A. The influence of childhood trauma and affective personality traits on neural correlates of reward anticipation. Presented at the 45th Annual Meeting of the International Neuropsychological Society in New Orleans, LA, February 1-4, 2017.
33. Bessette, K.L., Jenkins, L.M., Stange, J.P., **DelDonno, S.R.**, Skerrett, K.A., Kling, L., Maki, P. Weisenbach, S., & Langenecker S.A. Comorbid depression and anxiety has greater top-down and bottom-up neural emotional processing than depression alone in the remitted state. Presented at the 45th Annual Meeting of the International Neuropsychological Society in New Orleans, LA, February 1-4, 2017.

32. **DelDonno, S.**, Jenkins, L., Crane, N., Barba, A., Dion, C., Ryan, K., & Langenecker, S. Functional connectivity of the ventral striatum in remitted depressed individuals with and without substance abuse history. Presented at the 56th Annual Meeting of the Society for Psychophysiological Research in Minneapolis, MN, September 21-15, 2016.
31. **DelDonno, S.R.**, Jenkins, L.M., Crane, N.A., Nusslock, R., Ryan, K.A., Shankman, S.A., Phan, K.L., & Langenecker, S.A. Affective personality traits, reward behavior, and history of major depressive disorder predict altered functional connectivity in the ventral striatum. Presented at the National Network of Depression Centers Annual Conference in Denver, CO, September 12-14, 2016.
30. Jenkins, L., Barba, A., **DelDonno, S.**, Kling, L., Briceno, E., Weisenbach, S., Phan, L.K., Shankman, S., & Langenecker, S. Integrated cross-connectivity of amygdala, insula and subgenual cingulate predict superior facial emotion perception performance. Presented at the 71st Annual Meeting of the Society of Biological Psychiatry, Atlanta, GA, May 12-14, 2016.
29. **DelDonno, S.R.**, Barba, A., Feldhaus, C., Jenkins, L., Phan, L.K., Shankman, S., & Langenecker, S.A. Disrupted functional connectivity of the ventral striatum in young adults with remitted depression. Presented at the 71st Annual Meeting of the Society of Biological Psychiatry, Atlanta, GA, May 12-14, 2016.
28. Passarotti, A.M., Dominguez-Colman, L., **DelDonno, S.**, Trivedi, N., & Langenecker, S.A. Developmental differences in resting state signatures of approach-reward sensitivity in default mode, executive control and reward sensitivity networks. Presented at the 71st Annual Meeting of the Society of Biological Psychiatry, Atlanta, GA, May 12-14, 2016.
27. Passarotti, A.M., Srinivasan, V., Trivedi, N., Dominguez-Colman, L., **DelDonno, S.**, Patel, M., & Langenecker, S. Resting state neural signatures of approach-reward sensitivity in adolescents. Presented at the 62nd Annual Meeting of the American Academy of Child and Adolescent Psychiatry, San Antonio, TX, October 26-31, 2015.
26. Bhatt, T.S., Patel, P., Langenecker, S., **DelDonno, S.**, Sharma, K., & Jenkins, L. Neural mechanisms involved in mental imagery of slipping while walking: A preliminary fMRI study. Presented at the 45th Annual Meeting of the Society for Neuroscience, Chicago, IL, October 17-21, 2015.
25. **DelDonno, S.R.**, Jenkins, L.M., Skerrett, K., Hymen, E., Kreutzer, K., Broussard, N.G., Passarotti, A.M., Jacobs, R.H., & Langenecker, S.A. Impaired recognition of subliminal happy faces in remitted mood disorders. Presented at the 70th Annual Meeting of the Society of Biological Psychiatry, Toronto, Ontario, May 14-16, 2015.
24. Crane, N.A., Jenkins, L.M., Gowins, J.R., Barba, A.M., Gabriel, L.B., Kassel, M.T., Weldon, A.L., Baker, A.M., **DelDonno, S.R.**, Zubieta, J.K., Mermelstein, R.J., & Langenecker, S.A. History of substance use disorder modulates neural emotional processing in individuals with remitted major depression. Presented at the 70th Annual Meeting of the Society of Biological Psychiatry, Toronto, Ontario, May 14-16, 2015.
23. Crane, N.A., Gowins, J.R., Barba, A.M., **DelDonno, S.R.**, Jenkins, L.M., Meyers, K.K., Hazlett, K.E., Hsu, D.T., Mickey, B.J., Zubieta, J.K., & Langenecker, S.A. Independent component analysis of cognitive control as treatment predictors for major depressive disorder. Presented at the 43rd Annual Meeting of the International Neuropsychological Society, Denver, CO, February 4-7, 2015.
22. **DelDonno, S.R.**, Weldon, A.L., Passarotti, A.M., Mickey, B.J., Pruitt, P.J., Crane, N.A., Gabriel, L., Yau, W., Meyers, K.K., Hsu, D.T., Taylor, S.F., Heitzeg, M.M., Shankman, S.,

- Zubieta, J.K., & Langenecker, S.A. Reward-processing deficits in active but not remitted depression. Presented at the Annual National Network of Depression Centers Conference, Chicago, IL, October 22-24, 2014.
21. Crane, N.A., Gowins, J.R., Barba, A.M., **DelDonno, S.R.**, Jenkins, L.M., Meyers, K.K., Hazlett, K.E., Hsu, D.T., Mickey, B.J., Zubieta, J.K., & Langenecker, S.A. Cognitive control neural markers of treatment response for depression using independent component analysis. Presented at the Annual National Network of Depression Centers Conference, Chicago, IL, October 22-24, 2014.
 20. Jenkins, L.M., **DelDonno, S.R.**, Meyers, K.K., Zubieta, J.K., Starkman, M.N., & Langenecker, S.A. Effects of music on reward task performance during functional brain imaging. Presented at the Fifth Annual UIC Psychiatry Research Extravaganza, October 21, 2014.
 19. Langenecker, S.A., **DelDonno, S.R.**, Jacobs, R.H., Barba, A., Ryan, K.A., Gowins, J.R., Jenkins, L.M., Crane, N.A., Zubieta, J.K., Nusslock, R., Phan, K.L., & Shankman, S. Diminished learning and pursuit of reward and disrupted resting state connectivity of reward networks in remitted major depressive disorder. Presented at the Fifth Annual UIC Psychiatry Research Extravaganza, October 21, 2014.
 18. **DelDonno, S.**, Mickey, B., Weldon, A., Nagel, C., Pruitt, P., Yau, W., Zubieta, J., & Langenecker, S. Sex differential effects in psychomotor speed related to reward seeking and attainment. Presented at the 28th Annual Meeting of the Society for Research in Psychopathology, Evanston, IL, September 18-21, 2014.
 17. **DelDonno, S.R.**, Weldon, A.L., Meyers, K.K., Gabriel, L.B., Pester, B., Kassel, M.T., Crane, N., Hsu, D.T., Mickey, B.J., Zubieta, J., & Langenecker, S.A. Behavioral activation predicts reward-seeking in depression. Presented at the 69th Annual Scientific Meeting and Convention of the Society of Biological Psychiatry, New York, NY, May 8-10, 2014.
 16. **DelDonno, S.**, Kipman, M., Schwab, Z.J., & Killgore, W.D.S. The contributions of emotional intelligence and facial perception to social intuition. Presented at the Annual McLean Research Day, Belmont, MA, January 16, 2013.
 15. Dunning, J.P., **DelDonno, S.**, & Hajcak, G. The intersection of threat, anxiety, and affective startle modulation. Presented at the 52nd Annual Meeting of the Society for Psychophysiological Research, New Orleans, LA, September 19-23, 2012.
 14. **DelDonno, S.**, Schwab, Z.J., Kipman, M., Weber, M., & Killgore, W.D. Weekend sleep is related to greater coping and resilience capacities. Presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.
 13. **DelDonno, S.**, Weber, M., Kipman, M., Schwab, Z.J., & Killgore, W.D. Resistance to insufficient sleep correlates with olfactory cortex gray matter. Presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.
 12. Kipman, M., Weber, M., **DelDonno, S.**, Schwab, Z.J., & Killgore, W.D. Morningness-Eveningness correlates with orbitofrontal gray matter volume. Presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.
 11. Kipman, M., Schwab, Z.J., Weber, M., **DelDonno, S.**, & Killgore, W.D. Yawning frequency is correlated with reduced medial thalamic volume. Presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.

10. Weber, M., **DelDonno, S.**, Kipman M., Schwab, Z.J., & Killgore W.D. Grey matter correlates of daytime sleepiness. Presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.
9. Weber, M., **DelDonno, S.**, Kipman M., Schwab, Z.J., & Killgore, W.D. Grey matter correlates of self-reported sleep duration. Presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.
8. Schwab, Z.J., **DelDonno, S.**, Weber, M., Kipman, M., & Killgore, W.D. Habitual caffeine consumption and cerebral gray matter volume. Presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.
7. Killgore, W.D., Schwab, Z.J., **DelDonno, S.**, Kipman, M., Weber, M., & Rauch, S.L. Greater nocturnal sleep time is associated with increased default mode functional connectivity. Presented at the 26th Annual Meeting of the Associated Professional Sleep Societies, Boston, MA, June 9-13, 2012.
6. **DelDonno, S.**, Schwab, Z.J., Kipman, M., Rauch, S.L., & Killgore, W.D. The influence of cognitive and emotional intelligence on performance on the Iowa Gambling Task. Presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA, February 15-18, 2012.
5. Kipman, M., Schwab, Z.J., **DelDonno, S.**, & Killgore, W.D. Gender differences in the contribution of cognitive and emotional intelligence to the left visual field bias for facial perception. Presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA, February 15-18, 2012.
4. Kipman, M., Schwab, Z.J., Weiner, M.R., **DelDonno, S.**, Rauch, S.L., & Killgore, W.D. Contributions of emotional versus cognitive intelligence in humor appreciation. Presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA, February 15-18, 2012.
3. Killgore, W.D., Schwab, Z.J., Weiner, M.R., Kipman, M., **DelDonno, S.**, & Rauch, S.L. Overeating is associated with altered cortico-limbic responses to images of high calorie foods. Presented at the 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA, February 15-18, 2012.
2. Kipman, M., Schwab Z.J., Weiner, M.R., **DelDonno, S.**, Rauch S.L., & Killgore W.D. The insightful yet bitter comedian: The role of emotional versus cognitive intelligence in humor appreciation. Presented at the Annual McLean Research Day, Belmont, MA, January 11, 2012.
1. **DelDonno, S.** & Hajcak, G. The impact of threat of shock on the defensive startle reflex. Presented at the Stony Brook Undergraduate Research and Creative Activities Conference, Stony Brook, NY, April 27, 2011.

Research Experience

Graduate Research Assistant

2013 – 2018

University of Illinois at Chicago, Chicago, IL

Clinical Psychology Doctoral Program, Cognitive Neuroscience Center

Advisor and PI: Scott Langenecker, Ph.D.

- Author and co-author manuscripts for publication
- Develop and program fMRI tasks in E-Prime 2.0
- Pre-process and build first- and second-level models in SPM8 for functional and resting-state MRI data in longitudinal studies of active and remitted mood disorders
- Conduct structured and semi-structured diagnostic interviews; administer psychodiagnostic assessments of depression, suicidal ideation history, anxiety, social phobia, and OCD with study participants
- Administer and score neuropsychological assessments

Clinical Research Assistant

2011 – 2013

McLean Hospital, Belmont, MA

Social, Cognitive, & Affective Neuroscience Laboratory

PIs: William “Scott” Killgore, Ph.D., Scott Rauch, M.D.

- Coordinated randomized controlled trial of internet-delivered CBT for depression
- Compiled grant proposals to Department of Defense funding agencies
- Managed all regulatory, progress reporting, and IRB documentation required internally and by funding agencies
- Ran participants through study protocols, including cognitive and neuropsychological testing, structured clinical interviews, and fMRI data acquisition
- Analyzed behavioral and fMRI data for presentation at professional conferences; contributed to manuscripts for publication

Teaching Experience

Teaching Assistant

Psychology Department, University of Illinois at Chicago

Introduction to Psychology

2015

Abnormal Psychology

2016

Psychology of Women and Gender

2016

Developmental Psychology

2017

Field Work in Applied Psychology

2017-2018

Invited Talks

Applying to Clinical Psychology Internship Department of Psychiatry & Behavioral Neuroscience, University of Chicago	2018
Applying to Clinical Psychology Internship Clinical Psychology Program Brown Bag, University of Illinois at Chicago	2018
Affective Predictors of Disrupted Reward-Seeking in Depression Clinical Psychology Program Brown Bag, University of Illinois at Chicago	2015

Service

Ad-hoc journal review for Cognitive, Affective, and Behavioral Neuroscience	2017
Ad-hoc journal review for British Journal of Psychiatry	2019
Prospective student interviews Clinical Psychology Program, University of Illinois at Chicago	2015, 2017

Membership

Society for Psychophysiological Research
Society for a Science of Clinical Psychology
Phi Beta Kappa
Psi Chi

References available upon request.