Anticipatory Reward Deficits in Melancholia

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THESIS

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EEG	Electroencephalography
fMRI	Functional Magnetic Resonance Imaging
GAF	Global Assessment of Functioning
HES	Hamilton Endogenomorphy Subscale
HRSD	Hamilton Rating Scale for Depression
MDD	Major Depressive Disorder
SCID	Structured Clinical Interview for DSM-IV
SPSS	Statistical Package for the Social Sciences

SUMMARY

Dysfunctional reward processing has long been considered an important feature of major depressive disorder (MDD). However, empirical findings on reward processing and MDD remain mixed. Depression is a heterogeneous disease and the nature of this heterogeneity may contribute to the inconsistent empirical findings on reward dysfunction in MDD. The current study examined one source of heterogeneity, melancholic symptoms, and its association with reward processing. In 254 people, EEG alpha asymmetry was measured during a behavioral reward task as an indicator of reward processing. Melancholic depression was measured categorically (DSM diagnosis) and dimensionally (Hamilton Endogenomorphy Scale). Results showed that a categorical definition of melancholia did not predict reward processing; however, a dimensional definition did, with higher melancholic symptoms predicting reduced reward anticipation. Importantly, the effects of melancholic symptoms on reduced reward anticipation remained above and beyond overall depressive symptoms. These results suggest that dysfunctional reward processing may only be associated with melancholic symptoms, not depression in general. If replicated, this finding could have important implications for MDD treatment and intervention.

I. INTRODUCTION

Major Depressive Disorder (MDD) is a prevalent, costly and debilitating psychiatric illness (Kessler et al., 2005), for which treatments have only demonstrated moderate efficacy. It is therefore important to research the underlying mechanisms of MDD to better inform treatment and intervention development and study. However, within group heterogeneity in MDD can often hinder these research undertakings. For example, reward processing has been demonstrated as a major deficit in MDD, but some contrary findings suggest that reward dysfunction may not be a universal feature of all forms of depression as previously believed. The current study examines melancholia as a particular subtype/dimension within MDD and its association with a physiological correlate (frontal EEG alpha asymmetry) of reward anticipation during a monetary reward task.

A. Heterogeneity in Depression

Depression is a heterogeneous disease. By conservative estimates, there are at least 14,528 different combinations of symptoms possible to render a diagnosis of MDD (Zimmerman, Ellison, Young, Chelminski, & Dalrymple, 2015). Fried & Nesse (2015) examined 3703 patients from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study and found patients with MDD exhibited 1030 distinct symptom profiles. The symptom profile most shared among patients was only exhibited by 1.8% of the sample and almost half of all profiles were exhibited by only one person. These findings demonstrate the heterogeneous nature of MDD and suggest that individuals with depression may share the same diagnosis but have very few symptoms in common. Heterogeneity in MDD is inherently problematic. Individual symptoms or symptom clusters of MDD have been shown to differentially predict clinical indicators of depression including familial risk of MDD (Chen et al, 2000), comorbid

psychopathology (Lux & Kendler, 2010), and characteristics of the MDD episode (Harkness & Monroe, 2006). Taken together, the evidence suggests that within-group heterogeneity can lead to inconsistent findings and hinder research on biomarkers (Gillihan & Parens, 2011; Hyman, 2010), treatments, and prevention efforts.

B. Reward Processing in Depression

One of the ways to parse heterogeneity is to examine core features of the syndrome. Numerous theorists and clinicians have proposed that dysfunction in reward processing is a core feature of depression (Clark, Beck, & Beck, 1994; Clark & Watson, 1991; Davidson, 1992; Shankman & Klein, 2003). However, some contrary findings remain in the empirical literature on MDD and reward dysfunction (Reid et al., 1998; Pizzagalli et al., 2002). These mixed results suggest that reward dysfunction may not be a universal feature of depression as previously believed, but is instead associated with some symptom clusters within MDD.

In particular, melancholic MDD may demonstrate a distinct profile of reward deficits compared to other MDD subtypes. Melancholic depression is characterized by marked anhedonia, in which individuals almost completely lose interest in, or have practically no reactivity to, rewarding stimuli (APA, 2013). Melancholia first appeared in DSM-III (APA, 1980) and has been included as a subtype or specifier of MDD in subsequent versions of the manual. Some researchers have questioned the validity of melancholia as a qualitatively distinct subtype (Joyce et al., 2002; Kendler, 1997; Rush & Weissenburger, 1994). Kendler (1997) posited that melancholia is simply a more severe form of MDD, not etiologically separate from nonmelancholic MDD. Arnow et al. (2015) found no difference in treatment outcome between melancholia and other subtypes of MDD. On the other hand, factor analytic studies have identified melancholia as a distinct subtype of MDD (Kiloh & Garside, 1963, Marcos &

Salamero, 1990) and several other lines of evidence supports melancholia as a true phenotype (see review by Leventhal & Rehm, 2005). This debate reflects the difficulties in defining melancholia. Indeed, the symptom criteria for melancholia have been revised in nearly all revisions of the DSM. Despite ongoing changes, the impairment of the ability to anticipate or experience pleasure continues today as a central symptom of melancholic MDD. DSM5 (2013) states that in melancholia, "there is a near-complete absence of the capacity for pleasure, not merely a diminution (p185)." A blunted response to reward and pleasure is a key variable that also distinguishes melancholia from other subtypes of depression. For example, unlike the blunted positive affect seen in melancholic MDD, atypical MDD is primarily defined by mood reactivity, or improved mood in response to positive events.

Behavioral studies have demonstrated an association between melancholia and reward processing deficits. Day et al. (2015) used a facial recognition task and found that melancholic MDD was characterized by a loss of sensitivity to positive emotionality compared to non-melancholic MDD and healthy controls, even when controlling for MDD severity. Notably, these differences were specific to impairments in processing positive emotion and not problems in general emotion processing. Although not measuring melancholia per se, Vrieze et al. (2014) found reduced reward learning in MDD patients who were high in anhedonia compared with patients low in anhedonia. Taken together, these findings suggest that reward processing may be impaired in melancholic MDD and that it may be a specific feature of the subtype.

Reward processing is multifaceted and that there is a growing view that anticipatory reward processing is qualitatively different from consummatory reward processing (Klein (1974); Sherdell, Waugh, & Gotlib, 2012). Anticipatory reward processing is experienced pre-reward and represents a conscious desire for a stimulus whereas consummatory reward

processing refers to the pleasure derived from experiencing a stimulus. Limited evidence has suggested that while all individuals with depression experience deficits in reward processing, consummatory reward processing is specific to melancholia (Shankman, Sarapas, & Klein, 2011). Further investigation is needed to examine the role of melancholia in anticipatory reward processing.

C. Frontal Alpha EEG Asymmetry

One way reward processing has often been measured is with frontal electroencephalogram (EEG) alpha asymmetry. Examining EEG asymmetry as an indicator of reward processing stems from Davidson's approach-withdrawal model (see Shankman & Klein, 2003 for a review). Davidson et al. (1992, 1994, 1998) proposed that approach and withdrawal systems are lateralized in prefrontal regions of the brain. The model proposes that the left hemisphere is associated with the approach system, which controls appetitive and goal-directed behavior and responding to rewarding stimuli, and the right hemisphere is associated with the withdrawal system. Therefore, a frontal asymmetry characterized by greater brain activity in left frontal regions compared to right frontal regions is thought to indicate greater activity of the approach system.

One way that the relative activation of right and left frontal regions has been measured is via the relative difference in EEG alpha power (Allen et al., 2004; Coan et al., 2006). Alpha power is the frequency band between 8-13 Hz and is associated with "relaxed wakefulness," in which reductions in alpha occur when underlying cortical systems actively engage in processing (Davidson, 2004). This suggests that alpha power is *inversely* related to brain activity, and a common heuristic for measuring brain activation is therefore to measure *decreases* in alpha power (Coan et al., 2006; although see Tenke & Kayser, 2005 for a critical discussion of this

premise). “Frontal asymmetry” has therefore most typically been assessed by comparing right versus left frontal alpha power (with greater right than left alpha indicating greater left than right “brain activity”).

Resting EEG studies support Davidson’s proposed lateralization of approach and withdrawal processes in the brain (Davidson, 1998). Relative left prefrontal resting EEG asymmetry was found to be associated with greater self-reported BAS sensitivity (Sutton & Davidson, 1997). Additionally, baseline differences in anterior left activation predicted reward learning in a behavioral task in a non-clinical sample (Pizzagalli et al., 2005). Furthermore, resting EEG also captures approach and withdrawal processes in clinical samples such as individuals with MDD. One of the core features of Major Depressive Disorder (MDD) is a deficit in approach-related tendencies (Henriques & Davidson, 2000; Davidson, 1992). Consistent with this, several studies have shown that people diagnosed with depression exhibit a decreased relative left asymmetry as compared to healthy controls. Resting EEG activity has been associated with trait measures of positive affectivity (Harmon-Jones & Allen, 1997; Coan & Allen, 2003). In comparison to controls, individuals who are at risk for depression (Tomarken, Dichter, Garber, & Simien, 2004), currently experiencing depression (Thibodeau, Jorgensen, & Kim, 2006), and in remission from depression (Gotlib, Ranganath, & Rosenfeld, 1998; Stewart, Bismark, Towers, Coan, & Allen, 2010) all demonstrate reduced left relative to right frontal activity at rest. This pattern of asymmetry has also been observed when depression is measured dimensionally (Schaffer et al., 1983). Taken together, research on emotional tendencies and emotional responding broadly support EEG alpha asymmetry as an index of approach-related tendencies in both control and clinical samples.

In addition to measuring EEG at rest, researchers have measured EEG alpha activation during behavioral tasks that elicit reward processing (Shankman et al., 2007; 2013). According to the capability model of frontal EEG asymmetry (Coan et al., 2006), brain activation elicited during an emotional task will be a stronger, more reliable indicator of individual differences related to that emotion than activity recorded at rest, as it tests individuals' capacity to engage neural systems relevant to the emotional task. Frontal EEG asymmetry may therefore be more reflective of reward processing if measured during an affective challenge rather than at rest. When EEG is measured during an approach-related task, participants with early-onset depression differed from late-onset depression and non-depressed control individuals in frontal asymmetries while anticipating the possibility of a reward, suggesting specific deficits in approach motivation (Shankman, Klein, Tenke, & Bruder, 2007; Shankman et al., 2013).

Considering the problematic nature of heterogeneity in MDD, examining qualitatively different dimensions/subtypes of depressive symptoms may help clarify whether different symptom dimensions are associated with different patterns of reward processing. As melancholia is characterized by blunted reward processing, the current study will examine whether melancholic MDD is associated with an abnormal frontal EEG alpha asymmetry.

D. **Aims**

The main aim of the current study will be to test whether melancholic MDD demonstrates different patterns of frontal EEG asymmetry during reward anticipation compared to other depressive subtypes. As melancholic depression is characterized by a blunted response to reward, it is hypothesized that melancholic MDD will be associated with reduced left relative to right frontal brain activity compared to non-melancholic MDD and MDD-free controls. In contrast, non-melancholic MDD should demonstrate a similar frontal EEG asymmetry profile as controls;

however, it is also possible that non-melancholic MDD will show a reduced left relative to right asymmetry in brain activity than controls but not to the same degree as that of melancholic MDD.

Melancholia will be defined two ways - dimensionally and categorically. While the DSM defines melancholia as a subtype, there have been several studies showing that it may not identify valid subtypes that are etiologically distinct from non-melancholic depression (Kendler, 1997; Parker et al., 2009). Thus, along with a categorical conceptualization of melancholia, the present study will define melancholia dimensionally using the Hamilton Endogenomorphy Scale (HES; Thase, Hersen, Bellack, Himmelhoch, & Kupfer, 1983), an empirically derived subscale of the widely used Hamilton Rating Scale of Depression (HRSD) interview that captures the melancholic symptoms of depression.

II. METHODS

A. Participants

The present study uses data drawn from two samples and methods were previously described elsewhere (Shankman et al., 2007; 2013). Both studies used identical diagnostic assessment procedures and nearly reward tasks (the differences are noted below), but the former (N=99) was conducted in the New York area and the latter (N=155) was conducted in Chicago. In both samples, participants were over 18 and recruited from the community and area mental health clinics (total N= 254). The MDD groups consisted of 141 individuals with current MDD (38 melancholic, 103 non-melancholic), as defined by the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; American Psychiatric Association, 1994). The control group consisted of 113 non-MDD individuals who were required to have no lifetime diagnoses of MDD or dysthymia. All three groups were allowed to have current or lifetime anxiety disorders (see Table 1). Exclusion criteria included lifetime diagnosis of a psychotic disorder, bipolar disorder, or dementia; inability to read or write English; history of head trauma with loss of consciousness; and left handedness (as confirmed by the Edinburgh Handedness Inventory; range of laterality quotient: +20 to +100; Oldfield, 1971). All participants gave informed consent and were paid for their participation. All procedures were approved by the local institutional review boards.

B. Clinical Assessment

1. Clinical interview

Clinical diagnoses were determined using the Structured Clinical Interview for DSM–IV (SCID; First, Spitzer, Gibbon, & Williams, 1996). SCIDs were conducted by an experienced PhD-level interviewer or advanced PhD students supervised by a licensed clinical psychologist. Diagnosticians were trained to criterion by viewing the SCID-101 training videos (Biometrics

Research Department, New York, NY), observing two or three joint SCID interviews with an advanced interviewer, and completing three SCID interviews (observed by an advanced interviewer) in which diagnoses were in agreement with the observer.

2. **Hamilton Rating Scale for Depression**

Depression severity was measured using the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The HRSD is a 24-item, clinician-administered rating scale probing depressive symptoms on a 0 to 4 scale (symptom is absent, mild, moderate, or severe). The HRSD is widely used as a measure of depression severity and has high internal consistency (0.88; Rush et al., 2003), inter-rater reliability (0.80-0.98; Moberg et al., 2001), test-retest reliability (Williams, 1988) and validity (Hamilton, 2000). In the present sample, Cronbach's alpha was 0.92.

3. **Hamilton Endogenomorphy Scale**

Melancholic symptoms were measured dimensionally through the Hamilton Endogenomorphy Subscale (HES; Thase et al., 1983). The HES is a subset of items from the HAM-D and was designed to capture the symptoms of melancholic or endogenous MDD. These items include Middle Insomnia, Late Insomnia, Work and Activities (measure of anhedonia), Psychomotor Retardation, Psychomotor Agitation, Loss of Weight, Diurnal Variation (AM), and Hopelessness. The HES has been shown as a valid measure for diagnosing endogenomorphic depression and accurately determines DSM-III MDD subtypes (Thase et al., 1983). It is also strongly associated with diagnosis of endogenous depression as defined by the ICD-9 (Maier & Philipp, 1986). Cronbach's alpha for the HES was 0.75.

C. **Reward task**

A computerized slot machine paradigm (Shankman et al., 2007) was used to measure reward sensitivity. In this paradigm, three reels of numbers and fruits appeared on the screen and "spun" simultaneously for 11 s before they "landed" on a result. For each trial or "spin," participants pressed a button that corresponded to pulling a lever on the screen. The task included two conditions with 30 trials each (60 total): a reward condition (R) and a no-incentive condition (NI). During R, participants won money if the reels landed on three fruits. In contrast, during NI, participants did not win money regardless of the outcome. Thus, R was designed to elicit reward anticipation, whereas NI served as control for several aspects of R (e.g., visual input, anticipating an outcome). The amount of potential winnings during each R trial ranged from $0.30 to $0.45 in sample 1 and $0.50 to $3 in sample 2. Notably, participants never lost money in either condition if the reels did not land on three pieces of fruit.[1] Trials were divided into three blocks and presented in a pseudorandom order. There were never more than two consecutive trials of similar type or outcome. Participants began the task with $5 at site 1 and $2 at site 2 and were told the specific condition (R or NI) prior to each trial. The potential amount of winnings in each R condition was not disclosed.

D. **EEG Recording and Processing**

During the reward task, EEG data were recorded. In site 1, Electrodes were placed according to a modified version of the 10–20 system (Sharbrough et al., 1991). EEG was recorded from two homologous pairs of electrodes overlapping frontal (F3/F4; F7/F8), central

[1] There were also loss trials included (12 in site 1, 18 in site 2) in which participants lost money if the reels landed on three pieces of fruit. These trials were included to examine whether anticipation of losing money was related to withdrawal processes. This manipulation was ineffective, and the results from this condition are thus not discussed in this study.

(C3/C4; T7/T8), and posterior (P3/P4; P7/P8) brain regions over both left and right hemispheres and from one midline electrode (Cz) with a stretch-lycra electrode cap (Electro-Cap International, Inc., Eaton, OH; tin electrodes). The ground electrode was at the frontal pole (Fpz). Electrodes were placed at right supra- and infra-orbital sites to monitor for eye blinks and vertical eye movements and right- and left-outer canthi to monitor horizontal eye movements. In site 2, data were recorded using Ag/AgCl electrodes in a 64-channel stretch-lycra electrode cap (Compumedics Neuroscan 4.4, Charlotte, NC). The ground electrode was at the frontal pole (AFZ) and the online reference was near the vertex (between CZ and CPZ). Electrodes placed at the right supra- and infraorbital sites were used to monitor vertical eye movements (VEOG) and electrodes placed at the right and left outer canthi were used to monitor horizontal eye movements (HEOG). In both sites, electrode impedances were under 5,000 ohms, and homologous sites (e.g., F3/F4) were within 1,500 ohms of each other.

In site 1, data were recorded through a Grass Neurodata acquisition system (Grass Technologies, West Warwick, RI) at a gain of 10 K (5 K for eye channels) with a bandpass of 1–30 Hz. In site 2, data were recorded through a Neuroscan Synamp2 data acquisition system at a gain of 10K (5K for eye channels) with a bandpass of DC-200 Hz. In both sites, data were acquired and digitized using an EEG acquisition system (Neuroscan, 2003) continuously at a rate of 1000 Hz. EEG data were re-referenced offline by computing a digitally derived “linked mastoids” reference using data from the left and right mastoid.

EEG data from the 11-s period while the slot machine reels were spinning were segmented into consecutive 1.024-s epochs every 0.512 s (50% overlap). After referencing to a linked mastoid reference offline and then applying a baseline correction, we manually excluded epochs contaminated by blinks, eye movements, and movement-related artifacts from analyses

by direct visual inspection of the data. The EEG was tapered over the entire 1.024-s epoch by a Hanning window to suppress spectral side lobes. Artifact-free data were recovered in adjacent (overlapping) epochs and power spectra were computed offline from EEG data by using a fast Fourier transform. Subsequently, the average absolute alpha power was computed for each electrode site and then natural log transformed to normalize the data. Consistent with previous studies (e.g., Bruder, Fong, Tenke, & Leite, 1997), we defined the alpha band as 7.81–12.70 Hz and used it as an inverse measure of regional brain activity.

E. **Statistical Analysis**

Analyses were performed with SPSS version 22. Frontal EEG asymmetry scores were computed for the R and NI conditions by subtracting power of the average of left frontal electrodes from power of the average of homologous right electrodes (e.g., average of F4 & F8, subtracting the average of F3 & F7). Averaging power from neighboring electrodes helps yield a more representative frontal asymmetry score. These specific frontal channels were chosen, as they were common to both sites. Higher values on this "asymmetry" score reflected greater activity in left relative to right frontal regions.

ANOVAs were conducted to test the effect of MDD subtypes on reward sensitivity as measured by frontal EEG asymmetry scores. Covariates included in the analyses were site (site 1 vs. site 2), overall depression severity (total HRSD score), age and gender.

To test the aim of this study using the dimensional definition of melancholia, multiple regressions were conducted with frontal EEG asymmetry score as the dependent variable, and HES symptoms as the main predictor. Covariates included in the analyses were overall depression severity, site, age and gender.

In both analyses, diagnosis of an anxiety disorder and the study site were each tested for moderating effects on the relationship between melancholic symptoms and frontal EEG asymmetry.

III. Results

A. Demographic and clinical characteristics

Participants in the three groups (two MDD groups and non-MDD controls) did not significantly differ on age, $F(2,253) = 1.15$, *ns*, gender, χ^2 (2, N=254) = .88, *ns*, or ethnicity, χ^2 (2, N=254) = 4.12, *ns*. As expected, the control and two MDD groups differed on panic status, χ^2 (2, N=254) = 18.70, $p < .05$, MDD severity, $F(2,253) = 398.53$, $p < .05$, melancholic symptoms, $F(2,253) = 289.48$, $p < .05$, psychiatric medication, χ^2 (2, N=254) = 9.73, $p < .05$, and current functioning, $F(2,253) = 212.90$, $p < .05$. Melancholic and non-melancholic MDD groups did not differ on comorbid anxiety status, χ^2 (1, N=141) = .71, *ns*, psychiatric medication, χ^2 (1, N=141) = .39, *ns*, or current functioning $F(1,140) = 2.50$, *ns*. But melancholic MDD did present higher overall MDD severity, $F(1,140) = 6.44$, $p < .05$ and, as expected, higher melancholic symptoms, $F(1,140) = 9.32$, $p < .05$ than non-melancholic MDD.

B. Is melancholia associated with abnormal EEG asymmetry in anticipation of reward?

When melancholia was defined categorically, no significant effect of group was found on EEG asymmetry, $F(2,253) = .87$, *ns* (see Figure 1). Effects were not moderated by site, $F(2,253) = .72$, *ns*, or diagnosis of an anxiety disorder, $F(2,253) = .06$, *ns*.

When melancholia was defined continuously, as hypothesized, melancholic symptoms predicted frontal EEG asymmetry, $\beta = -.19$, $t(253) = -3.09$, $p < .05$. Depression severity also predicted frontal EEG asymmetry, $\beta = -.15$, $t(253) = -2.42$, $p < .05$. Importantly, when both melancholic symptoms and overall depression severity were entered in the same regression model, melancholic symptoms remained a significant predictor, $\beta = -.34$, $t(253) = -2.16$, $p < .05$ but depression severity dropped to non-significance, $\beta = .16$, $t(253) = 1.01$, *ns*. The main effect

of melancholia remained significant (β = -.37, $t(253) = -2.37$, $p < .05$) when controlling for age, gender, site, and depression severity (see Table 2). In addition, effects were not moderated by site, β = .02, $t(253) = .19$, *ns* or diagnosis of an anxiety disorder, β = .10, $t(253) = 1.20$, *ns*, so these interaction terms were not included in the final model.

Table 1. Demographics and clinical characteristics

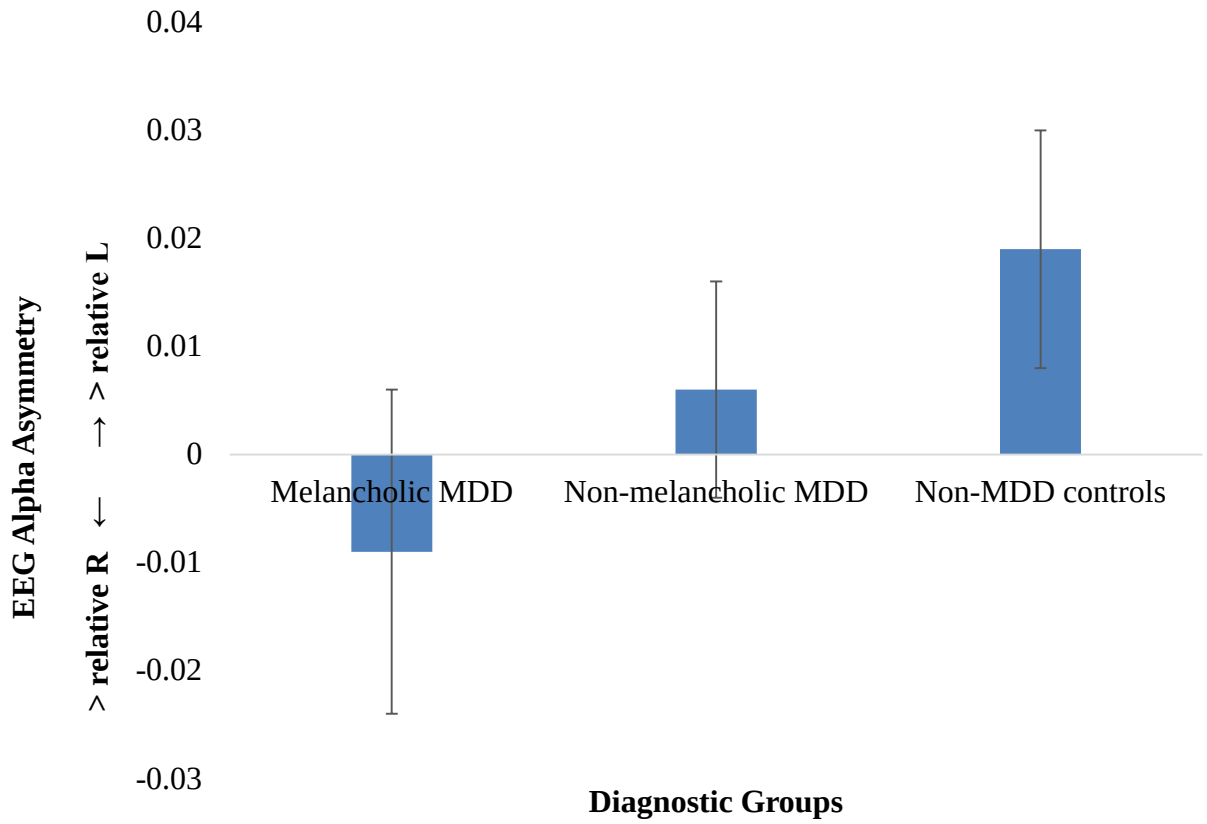
	Melancholic MDD (N=38)	Non-melancholic MDD (N=103)	Non-MDD controls (N=113)
Age (SD)	35.92 (12.86) [a]	32.79 (11.66) [a]	32.56 (12.50) [a]
Sex (% female)	60.53% [a]	68.93% [a]	66.37% [a]
Ethnicity (% white)	55.3% [a]	64.1% [a]	50.4% [a]
Lifetime anxiety disorder	52.63% [a]	44.66% [a]	21.24% [b]
Psychiatric medication	36.84% [a]	43.69% [a]	7.08% [b]
HRSD severity (SD)	29.00 (8.12) [a]	25.35 (7.38) [b]	3.21 (4.90) [c]
HES Melancholia subscale (SD)	9.00 (3.08) [a]	7.49 (2.42) [b]	1.11 (1.72) [c]
GAF (SD)	51.34 (6.70) [a]	53.44 (7.09) [a]	81.50 (14.51) [b]

Note. Different superscripts represent significant ($p < .05$) group differences

Table 2. Effect of melancholia on EEG asymmetry

Variable	*b*	*t*	*p*-value
Block 1			
Age	0.13*	2.02	0.04
Gender	0.02	0.29	0.78
Site	-0.02	-0.33	0.74
HRSD	-0.16*	-2.57	0.01
Block 2			
Age	0.14*	2.26	0.02
Gender	<0.01	0.13	0.90
Site	-0.03	-0.47	0.64
HRSD	0.18	1.14	0.26
HES	-0.37*	-2.37	0.02

Figure 1. Categorical group differences in EEG asymmetry



IV. Discussion

A. Summary

The aim of the current study was to investigate reward processing in melancholia. Prior research demonstrated reward processing deficits in individuals with major depression in general, but the studies are mixed. Heterogeneity in the samples of depressed individuals may have contributed to inconsistencies in such findings. As part of this heterogeneity, different symptoms or symptom clusters of depression may demonstrate different levels of reward dysfunction. As melancholic MDD is characterized by a blunted response to reward, melancholic symptoms may especially predict reward-processing deficits.

Consistent with our hypothesis, results demonstrated that melancholic depression when defined dimensionally (but not categorically) predicted reduced left relative to right frontal EEG activation during a reward anticipation task. These findings remained after, even when adjusting for covariates such as age, study location and comorbid anxiety disorders. As previously reported in these two samples (Shankman et al., 2007; Shankman et al., 2013), higher levels of depressive symptoms were also associated with reduced left relative to right frontal EEG activity. However, the effect of melancholia was not due to overall depression severity as melancholia remained significant even when depression severity was a covariate (and, of note, the effect of depression severity became non-significant after controlling for melancholic symptoms). That is, rather than being a general feature of depression, reward dysfunction, in particular reward anticipation deficits, may be specifically related to the melancholia and not all of MDD.

B. Behavioral Correlates of Melancholia

Presence of reward anticipation deficits in melancholia is consistent with prior findings on other unique psychological features of the subtype. Anhedonia is a central component of the

melancholic subtype and has been shown to predict onset and maintenance of MDD. Compared to other subtypes, Melancholic MDD has been associated with higher levels of anhedonia (Austin & Mitchell, 1995; Bracht et al., 2014; Day et al., 2015; Wacker et al., 2009). While anhedonia is a broad construct (Shankman et al., 2014), it is particularly noteworthy that those with melancholic MDD exhibit "motivational anhedonia," a term which emphasizes the reduced motivation to pursue rewards and positive stimuli (Treadway & Zald, 2011). In the present study, melancholic symptoms predicted a loss of sensitivity to signals of upcoming monetary rewards. Relatedly, Day et al. (2015) demonstrated that melancholic participants were distinguished specifically by impairments related to identifying happy faces (positive emotion), and did not show a global slowing or flattening of emotion processing, even in comparison to healthy controls. These results further support melancholia's specific deficits to positive or rewarding stimuli. Melancholia is also distinctive in its impairments in motivation and effort related to goal-pursuit. Rogers et al. (2004) found that melancholic MDD and non-melancholic MDD performed similarly on cognitive tasks such as the stroop task but the performance of those with melancholia suffered when faced with increased cognitive load of additional tasks. These findings suggest that the psychological profile of melancholic MDD is characterized by specific behavioral constructs including anhedonia and motivation. The current study adds to this literature and further identifies anticipatory deficits in reward as a feature of the melancholic subtype.

C. **Biological correlates of Melancholia**

In addition to the behavioral correlates of melancholia, melancholia is also characterized by unique biological variables compared to other forms of MDD. Melancholia has long been viewed as a type of MDD with a biological (rather than environmental) etiology (Klein, 1974).

For example, individuals with melancholic MDD demonstrate hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and increased cortisol production (Taylor & Fink, 2006). In addition, dopamine plays an important role in the pursuit of rewards (Treadway & Zald, 2011) and appears to be particularly abnormal in those with melancholic depression (Parker, 2007; Parker et al., 1995). Relatedly, melancholic MDD is associated with other specific clinical features such as psychomotor disturbance (Parker et al., 2010) and unique vulnerability markers such as blunted neural response to errors (Weinberg, Liu, & Shankman, under review). The present study further supports the presence of unique biological correlates in melancholia and specifically demonstrates abnormalities in frontal brain regions during reward, consistent with neuroimaging studies showing PFC abnormalities in melancholia (Korgaonkar et al., 2011; Pizzagalli et al., 2004).

Findings from previous EEG studies on melancholia have been mixed. In a resting EEG study, Quinn et al. (2014) found that melancholic MDD and controls did not differ whereas the *non-melancholic* MDD group exhibited greater relative left frontal activation. This finding was contrary to their hypothesis and somewhat unexpected. These puzzling results could be due to the limitations of the resting EEG design as it is a less powerful indicator of individual differences of "affective style" compared to EEG measured during an affective task (Coan et al., 2005). Extending the work of Quinn et al. (2014), the current study examines EEG activation during a reward task rather than at rest and thus may better capture group differences as it represents a 'probe' of the reward system.

A prior EEG study from our group using a subsample of the current report examining MDD heterogeneity found support for melancholia as a distinct subtype but only found group differences in posterior electrodes during consummatory reward (Shankman, Sarapas, & Klein,

2011). This finding was not replicated in the present study with a larger sample. Furthermore, only trend-level differences were found between melancholic MDD and controls in the original study. This may have been due to lack of statistical power due to a relatively small sample size of melancholic MDD (N=17).

D. Categorical vs. Dimensional Measures of Melancholia

The present study found significant effects when melancholia was defined dimensionally but not when it was defined categorically. One reason for the effect may be that the current categorical criteria for melancholic depression do not adequately capturing the melancholia subtype. Melancholia as defined by DSM criteria has been shown to have low in reliability (kappa = 0.11) and validity (Joyce et al., 2002). At the same time, evidence generally supports melancholia as a true phenotype (see review by Leventhal & Rehm, 2005). This contrasting evidence suggests that the current DSM criteria may not adequately represent the syndrome of melancholia (Parker et al., 1994; Parker et al., 1997).

Additionally, current DSM-defined MDD subtypes may fail to capture variance that may be accounted for by subthreshold subtype symptoms. Foti, Carlson, Sauduer, & Proudfit (2014) examined the effect of MDD heterogeneity on monetary reward sensitivity and found blunted reward sensitivity only in the MDD subgroup characterized by the single symptom of impaired mood reactivity. In contrast, Melancholic and atypical MDD subtypes, as defined by DSM criteria, did not significantly predict reward sensitivity. Similar to Foti et al. (2014), we did not find significant group differences on reward dysfunction based on DSM-defined subtypes. These results suggest that rather than examine MDD subtypes categorically, it may be more fruitful to examine subtypes dimensionally or even in terms of a single symptom. While Foti et al. (2014) found reward dysfunction specific to the symptom of mood reactivity, using a combination of

dimensional items such as the HES provides more reliability than relying on a single item. Present findings are generally consistent with Foti et al. (2014) as mood reactivity is a major component of melancholic MDD.

E. **Strengths and Limitations**

There were several notable strengths of the paper. Specifically, the present study included a heterogeneous population with comorbid anxiety and a wide age range. Including a broader experience of MDD gives us better external validity and account for the phenomenon of MDD as it would naturally occur – with psychiatric comorbidities over the lifespan. Furthermore, this approach allowed us to identify the absence of anxiety by depressive subtype interaction and further support reward anticipation deficits as a unique marker of certain types of MDD. The present study also utilized a large sample and examined both categorical and dimensional measures of melancholia. This dimensional approach allowed for the examination of melancholic symptoms even within non-MDD controls.

However, there were also several limitations. One limitation of the current study is the relatively small size of the melancholic subgroup (N=38). This may have contributed to the lack of significant categorical group differences. Another potential issue is the current sample's psychiatric medication use. Although the model adjusted for the effect of medication use, we did not have specific information on what type of medication individuals were taking. Thus even though we accounted for medication use, specific types of medication may have had an effect on the results. Lastly, we did not measure the inter-rater reliability of the melancholia diagnosis, so it's possible that variability between interviewers could have contributed to problems with accurately rating melancholia categorically. However, this is unlikely to be an issue as all raters were trained to criterion and demonstrated high overall agreement on the diagnostic interview.

F. Implications and Future Directions

The current study only examined the effect of MDD heterogeneity on reward anticipation. Future studies could explore the association between melancholia and other facets of reward processing, such as reward learning or willingness to work for rewards to determine more specific deficits in melancholia. Reward anticipation may be a unique feature of melancholic MDD and should be a target of intervention for treating this subtype. Additionally, melancholia may be better captured dimensionally than through DSM categories.

G. Conclusion

Findings support the idea that melancholia demonstrates a distinct profile of reward anticipation. Importantly, the present results support the validity of the melancholia subtype/dimension of MDD that is not simply a more severe form of MDD (Kendler, 1997). This research builds on previous literature on reward dysfunction in MDD and helps better understanding on the association by uniquely examining reward anticipation and MDD heterogeneity.

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Zimmerman, M., Ellison, W., Young, D., Chelminski, I., & Dalrymple, K. (2015). How many different ways do patients meet the diagnostic criteria for major depressive disorder? *Comprehensive Psychiatry, 56*, 29-34.

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EDUCATION

2013-Present **UNIVERSITY OF ILLINOIS AT CHICAGO** **Chicago, IL**
M.A. Clinical Psychology (2015)
Ph.D. Clinical Psychology (in progress)

2010 - 2011 **TEACHERS COLLEGE, COLUMBIA UNIVERSITY** **New York, NY**
M.A. Psychology in Education, Personality and Psychopathology track

2006 - 2010 **GRINNELL COLLEGE** **Grinnell, IA**
B.A. Major: Psychology, Concentration: Policy Studies

AWARDS

2015	ICPS Travel Award ($400)
2014	SSCP Student Poster Competition Distinguished Contribution Award ($100) Poster presented at the 26th annual APS convention: "Time course of threat responding in panic disorder"
2014 - 2015	UIC Travel Awards (multiple totaling $1,100 each year)
2010	Arthur Zankel Urban Fellowship ($10,000), Teachers College, Columbia University
2009	National Science Foundation Summer Research Institute in Experimental Psychology selected scholar ($2,400), University of South Carolina
2007	Summer Research with NIDA (National Institute on Drug Abuse) for Underrepresented Students selected scholar ($3,000), Washington University in St. Louis

PUBLICATIONS

1. Weinberg, A., **Liu, H.**, Proudfit, G. H., & Shankman, S.A. (in press). Blunted neural response to rewards as a vulnerability factor for anhedonic depression: Results from a family study. *Journal of Abnormal Psychology*.
2. Gorka, S.M., **Liu, H.**, Klein, D., Daughters, S., & Shankman, S.A. (in press). Is risk-taking propensity a familial risk factor for alcohol use problems? An examination in two separate samples. *Journal of Psychiatric Research.*
3. Gorka, S.M., **Liu, H.**, Sarapas, C., & Shankman, S.A. (in press). Time course of threat responding in panic disorder and depression. *International Journal of Psychophysiology.*
4. Yang, L.H., Tu, M., **Liu, H.**, & Opler, M. (2011). The role of subtypes in understanding disease processes within schizophrenia: Case example of 'deficit syndrome'. *Shanghai Archives of Psychiatry, 23,* 109-111.

Manuscripts under review

5. Weinberg, A., **Liu, H.**, & Shankman, S.A. (under review). Blunted neural response to errors as a trait marker of melancholic depression. *Biological Psychology*.
6. Nelson, B.D., **Liu, H.**, Sarapas, C., & Shankman, S.A. (under review). Intolerance of uncertainty mediates the relationship between panic and the startle reflex in anticipation of unpredictable Threat. *Journal of Experimental Psychopathology.*

CONFERENCE PRESENTATIONS

1. Lieberman, L., **Liu, H.**, Huggins, A.A., Gorka, S.M., Sarapas, C., Shankman, S.A. (2015, May). *Informant-reports but not Self-reports of Personality Predict Psychophysiological Indices of Positive and Negative Emotional Responding.* Poster to be presented at the 27th annual Meeting for the Association for Psychological Science, New York, New York.
2. **Liu, H.**, Sarapas, C., & Shankman, S. A. (2015, March). *Reward Processing as a Familial Risk Marker for Internalizing Psychopathology.* Poster presented at the first annual meeting of the International Convention of Psychological Science (under the auspices of Association for Psychological Science), Amsterdam, The Netherlands.

3. **Liu, H.**, Katz, A. C. Nelson, B. D., Sarapas, C., Gorka, S. M., Campbell, M. L. & Shankman, S. A. (2014, September). *The effect of melancholia and atypical depression on EEG asymmetry during reward processing.* Poster presented at the 28th annual meeting of the Society for Research in Psychopathology, Chicago, IL.
4. Shankman, S. A., Sarapas, C., Gorka, S. M., Campbell, M. L., Katz, A. C., **Liu, H.**, Lieberman, L., DeLizza, A. A., Hodges, A. M., & Huggins, A. A. (2014, September). Family study of reward and threat sensitivity in internalizing psychopathology. In S. Morris (Chair), *The NIMH Research Domain Criteria initiative: Overview and exemplars.* Symposium conducted at the 28th annual meeting of the Society for Research in Psychopathology, Chicago, IL.
5. Sarapas, C., **Liu, H.**, Huggins, A. A., DeLizza, A. A., Hogdes, A. M., & Shankman, S. A. (2014, September). *Biased attention to threat and familial risk for anxiety disorders.* Poster presented at the 28th annual meeting of the Society for Research in Psychopathology, Chicago, IL.
6. ***Liu, H.,** Gorka, S. M., Sarapas, C., & Shankman, S. A. (2014, May). *Time course of threat responding in panic disorder*. Poster presented at the 26th annual Association for Psychological Science convention, San Francisco, CA. *Student Poster Competition Distinguished Contribution Award
7. **Liu, H.,** Cadden, M.H., & Hayes, S.M. (2013, March). *Cardiorespiratory fitness associations with fMRI activity during episodic memory retrieval in young adults.* Poster presented at the Boston University Graduate Program for Neuroscience Recruitment, Boston, MA.
8. **Liu, H.**, & Pannu Hayes, J. (2012, November). *Neural correlates of emotion regulation in PTSD*. Poster session presented at the 28th Annual Meeting of the International Society for Traumatic Stress Studies, Los Angeles, CA.
9. Nguyen, K., Tu, M., **Liu, H.**, Li, V. (2012, August). *Effects of acculturation on explanatory models for schizophrenia among Chinese immigrants.* Poster session presented at the 120th annual American Psychological Association convention, Orlando, FL.
10. **Liu, H.**, Tu, M., Nguyen, K. (2012, May). *Westernization and its effects on Chinese immigrant caregivers of schizophrenics*. Poster session presented at the 24th annual Association for Psychological Science convention, Chicago, IL.
11. **Liu, H.**, & Pannu Hayes, J. (2012, April). *Emotional valence and brain activity in trauma exposed veterans*. Poster session presented at VA Research Week, Boston, MA.
12. Chen, M., **Liu, H.**, Wisco, B., Marx, B., & Pannu Hayes, J. (2012, April). *Neural correlates of memory suppression*. Poster session presented at VA Research Week, Boston, MA.
13. Cadden, M.H., **Liu, H.**, Verfaellie, M., & Hayes, S.M. (2012, April). *Influence of aerobic fitness on cognitive and brain function in young adults.* Poster session presented at VA Research Week, Boston, MA.
14. Tu, M., **Liu, H.**, Nguyen, K. (2012, February). *Impact of immigration and westernization on explanatory models of schizophrenia among Chinese immigrant families*. Poster session presented at the 29th annual Winter Roundtable Conference, New York, NY.
15. **Liu, H.**, Frantz, R., Pauker, R., & Hsu, Y. (2011, August). *Indigenous labeling as explanation for schizophrenic symptoms: How Chinese immigrant relatives cope with severe mental illness and its implications*. Poster session presented at the 119th annual American Psychological Association convention, Washington, DC.
16. Hagen-Atwell, H. & **Liu, H.** (2008, October). *Priming effects on perceptions of self-governance*. Talk presented at the Undergraduate Research Symposia in Biological Sciences and Psychology, annual meeting of the Midstates Consortium for Math and Science, Chicago, IL

CLINICAL EXPERIENCE

August 2013-Present **OFFICE OF APPLIED PSYCHOLOGICAL SERVICES** **Chicago, IL**

Assessment Clinician, Supervisor: Amanda Lorenz, Ph.D.

- Performed neuropsychological and psychodiagnostic assessments
- Interviewed clients (adult and child), selected and administered tests, interpreted and wrote up results, and communicated findings to colleagues, clients, and families.

Psychotherapist, Supervisors: Joanna Buscemi, Ph.D., Gloria Balague, Ph.D, Nancy Dassoff, Ph.D.

- Provided empirically-supported psychological treatments to individuals seeking treatment for a variety of psychological disorders, including major depressive disorder, generalized anxiety disorder, ADHD, and PTSD.

Intake Clinician, Supervisors: Gloria Balague, Ph.D., Nancy Dassoff, Ph.D.

TEACHING EXPERIENCE

August 2013-Present **University of Illinois at Chicago** **Chicago, IL**

Teaching Assistant

- Introductory Psychology (Fall 2013)
- Community Psychology (Fall 2014)
- Developmental Psychology Lab (Spring 2015)

PROFESSIONAL SERVICE

Journal of Abnormal Psychology, ad-hoc reviewer (with Dr. Shankman)
Psychological Science, ad-hoc reviewer (with Dr. Shankman)
Reviewer for 2013 APA Annual Convention, Division 35
Reviewer for 2012 Asian American Psychological Association conference