Multi level Analysis of Positive Valence Systems Across Mood Disorders

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I. BACKGROUND and SIGNIFICANCE

Historical background

Several issues exist with current mood disorder classification. First, offspring of parents with bipolar disorder (BPD) are at disproportionate risk for developing mood disorder spectrum conditions but also major depressive disorder (MDD) (Barnett & Smoller, 2009; Birmaher et al., 2009). Similarly, twin studies indicate that the genetic correlation between mania and depression is substantial (r=0.65), suggesting shared genetic influences (McGuffin et al., 2003). As a result, the use of categorical DSM diagnoses in genetic studies may hinder the identification of susceptibility genes. Second, up to 25% of individuals with MDD might have undiagnosed BPD (Angst et al., 2003; Smith et al., 2011), with rates reaching 50% in patients with treatment-resistant MDD (Sharma et al., 2005). Critically, a history of manic symptoms in patients with DSM-IV MDD was linked to a more morbid course of the illness, worse psychological functioning, and poorer life quality (Smith et al., 2011). Similarly, in the Munich Developmental Stages of Psychopathology, 41.4% of MDD individuals met criteria for subthreshold BPD (Zimmermann et al., 2009). These individuals had higher rates of familial history of mania, nicotine abuse, alcohol use disorders, and a greater risk to converting to BPD. Also, MDD individuals with sub-threshold manic symptoms were more likely than those with "pure" MDD to have a history of poor antidepressant response and hospitalization (Smith et al., 2009). Third, the need to develop diagnostic approaches that go beyond assessment of a history of hypomania or mania is acute. This is particularly true since many BPD patients are misdiagnosed with MDD even after having experienced mania or hypomania because their recollection of hypomania can be poor (Ghaemi et al., 2002).

Previous research

Mounting evidence from epidemiology, psychopathology, and genetics challenges the commonly held notion that MDD and BPD are easily distinguishable diagnostic entities. As emphasized by others, there are no obvious "points of rarity" in the symptom continuum between bipolar and unipolar disorders and subsyndromal states (Phelps et al., 2008). The possible clinical implications are large as antidepressants can be of limited benefit in the treatment of DSM-IV BPD, and in some cases, can have disastrous consequences (e.g., El-Mallakh et al., 2006; Sachs et al., 2007).

A central limitation of prior studies seeking to compare Positive Valence Systems (PVS) domains in mood disorders is the reliance on DSM diagnoses, which fails to capture the full dimensional range of a construct. In keeping with the research domain criteria (RDoC), the present proposal avoids this problem by capitalizing on our substantial database of studies using the Probabilistic Reward Task (PRT) to define our sample. First developed in 2005 (Pizzagalli et al., 2005), the PRT allows to objectively assess participants' propensity to modulate behavior as a function of reward and has been made freely available to 73 research groups (55 US groups, 18 international groups). We have assessed 988 participants using the PRT across 14 studies and 6 independent labs in different countries. This sample includes 821 healthy controls and 167 individuals with current or past unipolar or bipolar mood disorder or elevated depressive

symptoms (current MDD: n=102; past MDD: n=32; past BPD: n=18; elevated depressive symptoms: n=15). Our dataset is large enough to build a normative distribution, ensuring that we can recruit subjects for our neuroimaging measures (n=80) that sample the full range of reward learning performance, without incurring the expense of recruiting a very large sample. Using PRT data from healthy controls (n=821), we can empirically demonstrate two important features: **1)** on a group level, patients with unipolar and bipolar diagnoses show attenuated and potentiated reward learning during this task, respectively, and **2)** DSM diagnostic categories fail to capture subsets of patients from both groups; i.e., some patients with unipolar diagnoses display intact reward learning, and some patients with bipolar diagnoses show disrupted (abnormally high) reward learning

From decades of animal, neuroimaging, and lesion studies, it is now recognized that the brain employs distinct hierarchical learning systems, including pavlovian, model-based, and model-free systems (Balleine & O'Doherty, 2010; Daw et al., 2005; Wunderlich et al., 2009). Recently, computational models of neural circuits involved in model-free learning—often described as prediction-error learning—have been especially well characterized (e.g., Glascher et al., 2010; Pessiglione et al., 2006; Schultz et al., 1997). Specifically, behavioral and neuroimaging data suggest that individuals develop a prediction of how much reward they will receive by choosing a particular action, and then use outcome information to update or maintain this prediction. The degree of flexibility that individuals exhibit in their ability to accurately update their predictions in the face of new information is a critical parameter, and has been found to reflect striatal dopamine (DA) signals (Schultz, 1998; Tsai et al., 2009), which are measurable using functional magnetic resonance imaging (fMRI) (D'Ardenne et al., 2008; Cooper & Knutson, 2008; Pessiglione et al., 2006).

The disrupted reward processing in mood disorders involves abnormal functioning in the ventral striatum, dorsal striatum, anterior cingulate cortex (ACC), and medial prefrontal cortex (mPFC), as well as dysfunctional corticostriatal glutamate signaling, which can be assessed through various neuroimaging techniques (e.g., Aharon et al., 2001; Delgado, 2007; Kennerley et al., 2006; Jocham et al., 2012). In the current proposal, we will employ measures across four units of analysis to assess the behavioral and neural mechanisms of prediction-error ("PE") learning: baseline glutamatergic functioning, blood-oxygen-level-dependent (BOLD) fMRI PE signaling, event-related potential (ERP) PE signaling, and behavioral indices of reward learning.

Study rationale

The failure to accurately differentiate between bipolar and unipolar symptoms represents a crisis. Current assessments often fail to identify the risk of developing manic symptoms in bipolar patients who seek treatment during a depressive episode. Further, standard pharmacotherapy for unipolar depression can trigger or exacerbate manic symptoms (Almeida & Phillips, 2012; Cusin et al., 2007). Given that manic episodes can result in devastating financial, legal, and professional consequences as well as heightened risk for self-destructive behavior, the need to understand the pathophysiological mechanisms that differentiate unipolar and bipolar depressive symptomatology is crucial (Almeida & Phillips, 2012; Cusin et al., 2007; Valenti et al., 2012).

The current proposal was developed to address these limitations by taking a transdiagnostic approach focused on the key domain of Reward Learning within the PVS matrix. As summarized in the RDoC workshop proceedings, Reward Learning cuts across several DSM

diagnoses, and is described as "*a process by which organisms acquire information about stimuli, actions, and contexts that predict positive outcomes*". Reward and reinforcement learning has been strongly linked to a wide range of disorders, as well as individual symptoms involving anhedonia, substance use, impulsivity (e.g., Barch & Dowd, 2010; Mason et al., 2012; Robinson & Berridge, 2008).

II. SPECIFIC AIMS

a. Objectives and hypotheses

Specific Aim 1: To investigate reward learning across four units of analyses within the mood disorder spectrum. One hundred sixty (n=160) individuals seeking treatment for mood disorders at three mood disorder clinics will be enrolled, and screened with the PRT. Using normative control data from 821 control subjects, 50% (n=80) of this sample will be asked to return for subsequent study sessions. Importantly, subjects in this sub-sample will be selected so that each quintile of the normative distribution of reward learning is equally represented (n=16 per quintile). Symptom severity measures will also be acquired and used to ensure that at least 33% of the total sample exhibits some degree of manic/hypomanic symptoms or severe depression. This sub-sample will then be further tested across four units of analysis: molecules, circuits, physiology, and behavior. Data will also be collected on 32 healthy controls, who will serve as a reference point for all measures.

Hypothesis 1: We will identify the units of analysis that show the strongest relative loading onto 3 reward-relevant symptom assessments in the areas of anhedonia, impulsivity, and mania across patients and controls.

Specific Aim 2: To investigate the predictive validity of reward learning units in a naturalistic follow-up study.

Hypothesis 2a: Relative weights for each unit of analysis for each symptom assessment area derived in Aim 1 will be used to predict the presence of anhedonic, manic and impulsive symptoms as assessed via phone interview at 3- and 6-month follow-up intervals. We predict that our units of analysis will have significant incremental predictive validity in predicting these domains while controlling for baseline severity.

Hypothesis 2b: Individuals who present at baseline with depressive symptoms but show an elevated response bias and enhanced PE signaling will show less symptom improvement following SSRI treatment in a naturalistic design (i.e., there is no treatment component to the study, but it is expected that many patients recruited through clinics will be receiving SSRI treatment).

III. SUBJECT SELECTION

a. Inclusion and exclusion criteria

General Exclusion Criteria

1) Suicidal ideation where outpatient treatment is determined unsafe by the study clinical interviewer. These patients will be immediately referred to appropriate clinical treatment;
2) Pregnant women or women of childbearing potential who 1) have not completed a negative urine pregnancy test prior to the MRI scan and/or 2) are seeking to become pregnant or believe that they may be pregnant

3) Serious/unstable medical illness (e.g., cardiovascular, renal, endocrine, neurologic disease);

4) Clinical or laboratory evidence of hypothyroidism;

5) History of seizure disorder, history or current diagnosis of dementia, score < 26 on the MMSE at screening;

6) History or current diagnosis of the following DSM-IV psychiatric illness: organic mental disorder, schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorder NOS, patients with mood congruent or mood incongruent psychotic features

7) Lifetime history of stimulant dependence (e.g., cocaine, amphetamines)**;

8) Current use of Methylphenidate (Ritalin) and other ADHD medications with dopaminergic effects**;

9) Patients who have had electroconvulsive therapy (ECT) in the past 2 years;

10) Failure to meet standard MRI safety requirements;

[** These exclusion criteria are included due to the proposed focus on reward learning, which relies on dopaminergic-rich brain circuitry and would thus be strongly affected by lifetime stimulant dependence and current treatment with methylphenidate or other ADHD medications.]

Inclusion Criteria: Mood Disorder Patients (n = 160)

1) Non-psychotic individuals seeking treatment at the Mass General Hospital (MGH) Depression Clinical and Research Program (DCRP), MGH Bipolar Clinical and Research Program (BCRP), and McLean Hospital Bipolar Disorder Program

2) Written informed consent;

3) Both genders and all ethnic origins, age between 18 and 65;

4) Right-handed (Chapman and Chapman, 1987);

5) Normal or corrected-to-normal vision and hearing

6) Absence of current illicit drug use (cocaine, amphetamines and cannabis) as assessed by urine drug test.

7) Stable medication over the past 8 weeks OR absence of any psychotropic medications for at least 2 weeks (for follow-up analyses testing effects in medication-free patients):

- 6 weeks for fluoxetine,
- 6 months for neuroleptics,
- 2 weeks for benzodiazepines,
- 2 weeks for any other antidepressants
- 4 weeks for any mood-stabilizers

Inclusion Criteria: Healthy Controls (n = 32)

Absence of medical, neurological, and psychiatric illness (including alcohol and substance abuse), as assessed by subject history and a structured clinical interview (SCID-I/NP).

2) No family history of mood disorders;

3) Written informed consent;
4) Both genders and all ethnic origins, age between 18 and 50;
5) Right-handed (Chapman and Chapman, 1987).

6) Normal or corrected-to-normal vision and hearing

7) Absence of current illicit drug use (cocaine, amphetamines and cannabis) as assessed by urine drug test.

8) No psychotropic medication.

b. Source of subjects and recruitment methods

Subjects will be recruited via flyer postings, Craigslist advertisements, clinicaltrials.partners.org, the Laboratory for Affective and Translational Neuroscience's recruitment website (www.mcleanstudies.org), advertisements on the MBTA subway interior, postcards, advertisements on college job websites, RSVP for Health, a Partners IRB-approved database of community individuals who have indicated that they want to be contacted by RSVP for Health for research studies, on WeSearchTogether.org, an NIMH-funded national registry that provides researchers with a free opportunity to connect with people living with mood disorders who are considering participating in research and an online advertisement campaign via TrialSpark, a Partners-approved recruiting system that helps investigators recruit patients/participants for clinical trials more efficiently using social media, software, and machine learning. Subjects will be recruited from: (1) the community; (2) outpatient clinics for depression and bipolar disorder at McLean Hospital; (3) the Depression Clinical and Research Program (DCRP) at MGH; and (4) the Bipolar Clinical and Research Program (BCRP) at MGH. Participants responding to ads may either complete an online screening tool on REDCap, a Partners secure website, be screened over the phone by study coordinators, or both. Flyer postings will include a QR code that can be scanned with certain mobile operating systems and direct the user to the REDCap online screening survey. Identifiable healthcare information will not be created for respondents who will likely not meet eligibility criteria (i.e. individuals outside the eligible ages and individuals who live too far from McLean).

Patient recruitment will be performed at the MGH DCRP and BCRP under the supervision of Drs. Fava and Nierenberg, respectively, and at the McLean Hospital Schizophrenia and Bipolar Disorder Program under the supervision of Dr. Ongur. Healthy controls will be recruited by members of Dr. Pizzagalli's laboratory, which is located in the Center for Depression, Anxiety and Stress Research at McLean Hospital. Prospective healthy control subjects will undergo a phone screen, which will include an overview of study details along with questions to assess inclusion/exclusion criteria. Eligible individuals will be invited to Dr. Pizzagalli's lab to complete two testing sessions involving computer tasks (such as the PRT), clinical interviews, an EEG session and a neuroimaging session. Informed consent will be collected at these sessions. **Importantly, no subject will be asked to delay or stop treatment for the purpose of participating in the studies described in this proposal**.

IV. SUBJECT ENROLLMENT

a. Methods of enrollment

One hundred sixty (160) individuals between 18 and 65 years old who meet all inclusion and exclusion criteria and are currently experiencing depressive and/or manic or hypomanic symptoms will be recruited from the Depression Clinical and Research Program (DCRP; Director: Maurizio Fava) and the Bipolar Clinical and Research Program (BCRP; Director: Andrew Nierenberg) at Massachusetts General Hospital (MGH). Additional recruitment will occur from the Schizophrenia and Bipolar Disorder Program (SBDP; Clinical Director: Dost Ongur) and Center for Depression, Anxiety and Stress Research (CDASR; Director: Diego Pizzagalli) at McLean Hospital. After providing written informed consent, these patients will first perform a computer task, the Probabilistic Reward Task (PRT), to determine their eligibility to continue in the study. Of the 160 patients screened, 80 will be brought back for further testing. In addition to this patient sample, 32 psychiatrically healthy individuals will be enrolled from the community.

All subjects will be carefully screened for MRI contraindications before completing magnetic resonance spectroscopy (MRS)/MRI sessions. Because the safety of MRI for fetuses has not been established, women who are pregnant or suspect they may be pregnant will be excluded. To ensure that there is no possibility that a subject might be pregnant; a urine pregnancy test will be administered prior to the MRI scan for all female subjects of childbearing potential. Only right-handed individuals will be enrolled, in order to elicit maximally uniform neural responses during the fMRI sessions and facilitate group averaging. Consistent with prior protocols, subjects will be asked to refrain from the use of illegal substances, and legal substances such as alcohol, for 24 hours prior to all sessions, which will be confirmed through administration of a urine drug screen. If the subject tests positive for a substance or refuses to provide a sample, they will be excluded from the remainder of the study and will be compensated for the portion of the study that they have completed. The results of the urine drug test will not become part of the participant's medical record. If a participant tests positive for a substance, but denies substance use, the participant will be given the opportunity to perform a second urine drug test. This procedure is in case of a false positive result.

The research will be conducted at MGH (recruitment and computer task screening) and McLean Hospital (biobehavioral testing).

b. Procedures for obtaining informed consent

At the beginning of session one, patients recruited through the DCRP, BCRP, SBDP and CDASR will be consented by on-site study staff members. Patients will read and sign an IRB-approved consent form detailing the general purposes and procedures of the experiment, and any questions they have will be answered. To participate in any of the proposed studies, an individual must be judged capable of understanding the nature of the research and the risks and potential benefits, which will be determined by a qualified study staff member. The consent form will clearly state that the subject may stop participation at any time without penalty. Potential risks and benefits will be explained by the project staff, and the subjects will be asked to sign the consent form. A member of the study staff will also sign the consent form. Following each session, the purpose of the research will be fully explained to the subject, and any additional questions will be answered.

Moreover, following each session the subject will complete a short form asking them for their introspections and comments.

Healthy control participants recruited through the community will first receive a phone screen, and then be invited to come to the PI's lab at McLean. Upon their arrival, consent procedures for healthy controls will proceed in the same manner as described in the preceding paragraph.

c. Treatment assignment, and randomization

Not applicable.

V. STUDY PROCEDURES

a. Study visits and parameters to be measured

This study will include five sessions: a screening session, a behavioral session, a neuroimaging session, and two follow up interview sessions.

Session 1 (Screening Session)

The first session will take place at any of the following locations: the DCRP at Massachusetts General Hospital (MGH),, the BCRP at MGH, the SBDP at McLean Hospital, or the CDASR at McLean Hospital. This session will involve consenting, urine drug screen, a saliva sample, PRT data collection and characterizing subjects based on their PRT performance, self-report questionnaires (demographics and Beck Depression Inventory – II) and clinician-administered measures. If a clinical subject has not already had a Structured Clinical Interview for DSM-IV (SCID; First et al., 2002; the SCID is a clinician-administered diagnostic tool that assesses the presence of Axis I disorders) within the past month, this will also be conducted by a trained clinical interviewer during the initial screening session to confirm that some level of mood disorder symptomatology is evident. The SCID clinical interviewer will also score the Young Mania Rating Scale and the Quick Inventory of Depressive Symptomatology (QIDS-C; Rush et al., 2003; the QIDS-C is a clinician-administered 16-item inventory that assesses depressive symptom severity) at this visit. Patient subjects who are deemed eligible based on their PRT data but who cannot take part in the EEG or MRI will complete the following self-report clinical assessments that would have been administered at the EEG session: the Inventory of Depressive Symptomatology (IDS; Rush et al., 1996; the IDS is a self-rated depression symptom severity rating scale); Medical Outcome Survey-Short form (SF-36; McHorney et al.,1993; the SF-36 is a measure of physical functioning, physical role functioning and social functioning); Quality of Life (Q-LES-Q; Endicott et al., 1993; the Q-LES-Q measures patient satisfaction and enjoyment across domains); Mood and Anxiety Symptom Questionnaire (MASQ; Watson et al., 1995; the MASQ is a self-report assessment of anhedonic depression, anxiety symptoms, and general distress); Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2007; the TEPS is a self-report assessment of anticipatory and consummatory (in-the-moment) pleasure experiences); the Perceived Stress Scale (PSS; Cohen et al., 1983; the PSS is a self-report assessment of the degree to which situations in one's life are appraised as stressful within the past month) the MGH Antidepressant Treatment Response Questionnaire (ATRQ; Chandler et al., 2009; the ATRQ assesses treatment history and medication use); the Chapman Handedness Inventory (CHI; Chapman & Chapman, 1987; the CHI is a self-report assessment of handedness); a General Habits Questionnaire (GHQ; the GHQ is a self-report assessment of caffeine intake); a Menstrual Cycle Questionnaire (MCQ; the MCQ is a self-report

of menstrual cycle patterns); the Barratt Impulsiveness Scale (BIS; Patton, Stanford & Barratt, 1995) and the Beck Depression Inventory – II (BDI-II; Beck, Steer, & Brown, 1996; the BDI-II is a self-report assessment of depressive symptomatology).

These questionnaires will be administered through the online survey program, REDCap Survey. In collaboration with the Harvard Catalyst, The Harvard Clinical and Translational Science Center, REDCap and REDCap Survey are free, secure, web-based applications hosted by the ERIS Team and designed to support data capture for research studies. The system was developed by a multi-institutional consortium initiated at Vanderbilt University. Data collection is customized for each study or clinical trial by the research team with guidance from ERIS REDCap administrators. REDCap is built around HIPAA guidelines but is not yet 21 CFR Part 11 compliant (Lynn Simpson, ERIS' EDC Support Specialist, is leading the PHS collaboration with Vanderbilt in development of this module).

Control subjects will complete the SCID, as well as the Mini Mental State Exam. This session is expected to take 2-3 hours for patients and 2 hours for controls, allowing 15 minutes for the consent process, 15 minutes for the urine drug test, 15 minutes for questionnaires,45 minutes to complete the PRT, and variable time for the SCID (approximately 30 minutes for control subjects and an hour for patients).

PRT Data Collection and Scoring

Probabilistic Reward Task: The probabilistic reward task (PRT) used in our prior work (see below) will be administered. The PRT has been successfully used by the PI to assess reward responsiveness (e.g., Pizzagalli et al., 2005, 2008b,c). In each trial, subjects choose which of two difficult-to-differentiate stimuli was presented. Stimuli consist of simple cartoon faces (diameter: 25 mm; eyes: 7 mm) presented in the center of the monitor. At the beginning of the trial, the face has no mouth. After a given delay, either a straight mouth of 11.5 mm ("short mouth") or 13 mm ("long mouth") is presented for 100 ms. Subjects are instructed to press an appropriate button to decide whether a long or small mouth had been presented. Unbeknownst to subjects, correct identification of one stimulus ("rich stimulus") is rewarded three times more frequently (*"Correct! You won 20 cents"*) than the other ("lean") stimulus. In healthy controls, this reinforcement schedule leads to a response bias (i.e., a preference for the more frequently rewarded stimulus). The degree of response bias toward the more frequently reinforced alternative will be used for operationalizing sensitivity to reward.

For patient participants (n=160), data from the PRT will be immediately classified relative to norm-referenced data from our normative database, using a gender-specific cutoff for each quintile to determine subject eligibility to continue in the study. From the initial sample of 160 participants who completed the screening session including the PRT, 50% (80) will be selected to continue for the behavioral and neuroimaging sessions. Importantly, subjects in this sub-sample will be selected so that each quintile of the normative distribution of reward learning is equally represented (n=16 per quintile). For comparison to the treatment-seeking individuals with mood disorders, 32 psychiatrically healthy and demographically matched individuals will be recruited and will also complete the PRT.

Participants will be observed with HIPAA-compliant teleconferencing software 'blue jeans' or 'vidyo' as they complete the PRT in order to verify compliance with task instructions while not impacting performance by directly observing from the same room. Video will not be recorded, only streamed.

Saliva Sample Collection and Analysis

During the Screening Visit, after participant eligibility is established, an additional saliva sample will be collected using Oragene DNA Collection Kit (DNA Genotek, Ottowa, Canada; http://www.dnagenotek.com/). The participant will be asked to spit into the collection tube to the fill line (2mL sample) and close with a stopper. The samples will be assayed for genetic information by the Smoller Laboratory (Director: Dr. Jordan W. Smoller) in the Psychiatric & Neurodevelopmental Genetics Unit at Massachusetts General Hospital, which provides core services for genetic assays.

Session 2 (Behavioral Session)

Contingent on subject availability, the second session will be scheduled within one week following session one and will take place at the Center for Depression, Anxiety, and Stress Research at McLean Hospital (Director: Diego Pizzagalli, Ph.D). This session will involve short clinical assessments, two measures of impulsivity (Hayling Sentence Completion Task and Richards Delay Discounting Task), self-report questionnaires, and an EEG recording during which participants perform the PRT for a second time as well as the Sensitivity to Temporal Variation in Reward (STVR) task. We will also ask participants for a urine sample to perform a urine drug test. If the subject tests positive for a substance or refuses to provide a sample, they will be excluded from the remainder of the study and will be compensated for the portion of the study that they have completed. The results of the urine drug test will not become part of the participant's medical record. If a participant tests positive for a substance, but denies substance use, the participant will be given the opportunity to perform a second urine drug test. This procedure is in case of a false positive result. Session 2 is expected to take 3.5 hours, allowing 2.5 hours for the EEG set-up, completion of the PRT and STVR, and 1 hour for the clinical assessments, impulsivity measures and self-report questionnaires.

Clinical Assessments

These clinical assessments include measures that we predict will capture symptoms related to reward learning, as well as symptom measures that we expect will not be related to reward learning, which we include in order to test the specificity of our biological and behavioral measures. The assessments administered include: IDS; Bipolar Inventory of Symptoms Scale (BISS; Bowden et al., 2007; the BISS is a 44-item scale designed to encompass the spectrum of behavioral disturbances in BPD); Clinical Global Impressions-Severity (CGI-S) and Improvement (CGI-I; Guy, 1976); SF-36; Q-LES-Q; MASQ; TEPS; PSS; ATRQ; CHI; GHQ;, MCQ; BDI-II; the ADHD subscale of the MINI (a clinician-administered assessment of lifetime ADHD symptomatology); BIS (Patton, Stanford & Barratt, 1995) and the Young Mania Rating Scale (YMRS; Young et al., 1978; the YMRS is a clinician-rated measure of current manic symptoms) at this visit to quantify the severity of (hypo)manic symptoms.

Self-report questionnaires will be administered on paper and/or through REDCap Survey.

Impulsivity Measures

Hayling Sentence Completion Test: The Hayling Sentence Completion Test (Burgess & Shallice, 1997) is used as a measure of cognitive inhibition. The task is divided into two conditions that each contain 15 sentences with the final word missing. Part A is an initiation condition in which participants are asked to say a word that completes the sentence, requiring activation of a strongly stereotyped automatic response (e.g., 'He posted a letter without a…stamp'). Part B is an inhibition condition where participants are required to inhibit the stereotyped response and say a word which does not complete the sentence (e.g., 'The captain wanted to stay with the sinking…orange'). Participants' response latencies for both sections are recorded, as well as the degree to which responses given in Part B relate to the probe sentence. Scaled scores will be obtained by adding response latencies in Part A and B, as well as response errors in each section (i.e., inappropriate responses).

Richards Delay Discounting Task: The Richards Delay Discounting Task (Richards et al., 1999) is used to determine indifference points for five different delay intervals. The program presents a series of questions that ask participants to decide between one amount of money that would be rewarded immediately and a second larger amount to be awarded after a certain delay. The larger amount of money is adjusted up or down by the program depending on participant's responses to previous questions. Adjustments are made so as to narrow the range of values on successive trials until an indifference point is arrived at. The indifference points for all five delay periods are used to calculate a delay discounting curve. Prior research suggests that impulsive individuals have steeper delay discounting curves.

EEG Recording

The PRT that was administered in session one will be administered again in session two, with the addition of 128-channel ERP recording in an acoustically/electrically shielded EEG booth in the PI's lab. The 128-channel EEG will be recoded using the Geodesic EGI system in an electrically shielded room. To avoid carry-over or learning effects, two different versions of the PRT that utilize different stimuli will be used for the screening and behavioral sessions. In the second version, instead of determining the length of the mouth, participants will need to decide whether a long or short 'nose' had been presented on the cartoon face by pressing the appropriate button. All other task parameters remain identical. Subjects will also complete a delay discounting task during EEG recording.

Sensitivity to Temporal Variation in Reward Task:

After the PRT, we will administer the STVR, a test of sensitivity to temporal variation in reward. This is a modified version of the 'Door Task' (Hajcak, Moser, Holroyd & Simons, 2006). Subjects engage in a guessing game where they start with two envelopes. They are told that the contents of one envelope will be paid to them immediately at the end of the session, and the contents of the other envelope will be paid to them in one month time, via a check in the mail. They can add to each envelope by playing a guessing game in which they are repeatedly presented with a graphic of two white envelopes and have to choose one to open. Immediately after choosing the envelope it changes color to either blue or orange. Subjects are told that blue means that this is an 'immediate' trial, in which the outcome will be added (or subtracted) from their 'immediate envelope' and orange means that this is a 'delayed' trial, in which the outcome will be added (or subtracted) from their 'delayed envelope'. Following this, an up or down

arrow is displayed to show whether it they received a reward or a penalty. There are a total of 240 trials (120 trials in which they win 50 cents and 120 trials in which they lose 25 cents). During the task feedback-related negativity to the up and down arrows is measured and used to indicate the degree to which subjects show phasic dopaminergic firing to immediate and delayed rewards and penalties. The total test time is approximately 30 mins. Participants are paid $16.25 at the end of this task.

Session 3 (Neuroimaging Session)

Contingent on subject availability, the third session will be scheduled within one week of session two. This session will take place at the McLean Hospital Imaging Center, and include structural MRI, functional MRI (fMRI) and MRS measures. Because the safety of MRI for fetuses has not been established, women who are pregnant or suspect they may be pregnant will be excluded. To ensure that there is no possibility that a subject might be pregnant; a urine pregnancy test will be administered prior to the MRI scan for all female subjects of childbearing potential. Pregnant women or women of childbearing potential who 1) have not completed a negative urine pregnancy test prior to the MRI scan and/or 2) are seeking to become pregnant or believe that they may be pregnant will be excluded from the remainder of the study and will be compensated for the portion of the study that they have completed. We will also ask all participants for a urine sample to perform a urine drug test. If the subject tests positive for a substance or refuses to provide a sample, they will be excluded from the remainder of the study and will be compensated for the portion of the study that they have completed. The results of the urine drug test will not become part of the participant's medical record. If a participant tests positive for a substance, but denies substance use, the participant will be given the opportunity to perform a second urine drug test. This procedure is in case of a false positive result. All MRI data will be collected on the 3T MR scanner. This session is expected to take a total of 120 minutes, assuming 90 minutes in the scanner and 30 minutes beforehand to prepare subjects, complete a pregnancy test if needed and do the impulsivity tasks.

During the structural and MRS scans, subjects will be instructed to rest quietly with their eyes open, so as to prevent drowsiness or falling asleep. During the fMRI portion of the scanning session, participants will complete a reinforcement learning task (Pessiglione et al., 2006) during fMRI. This task provides an additional assessment of reward learning that has been found to probe cortico-striatal circuitry during fMRI. The task is a first-order probabilistic instrumental learning task with monetary outcomes. In this task, participants are instructed to choose between two novel visual stimuli displayed on a computer screen, so as to maximize payoffs. Each of the stimulus pairs (gain, loss, neutral) will be associated with a given outcome (gain: win $10 or $0; loss: lose $10 or $0; neutral: look at $10 bill or nothing). For the gain pair, the probabilities of winning $10/$0 will be 80/20% for one stimulus and 20/80% for the other. Similarly in the loss pair, the probabilities of losing $10/$0 will be 80/20% for one stimulus and 20/80% for the other. In the neutral pair, there will be no financial outcome (subjects look at an image of a $10 bill in one outcome or at nothing in the other one, but they will be told that there will be no monetary consequences in these trials). For each trial, one pair will be randomly presented, with one stimulus above and one below a fixation cross (counterbalanced). The subject will be instructed to choose the upper or lower stimulus by pressing one of two keys. After 4 seconds the choice will be circled

in red and the outcome (either "Nothing", "Gain", "Loss" or "Look") will be presented, accompanied by the image of a $10 bill in the event of gain, loss and look outcomes. In sum, to win money the subjects have to learn, by trial and error, the stimulus-outcome associations. The task will involve four 10-min blocks, each containing new stimuli to be learned and 90 trials (30/condition). To minimize the possibility that participants use verbalization strategies to learn the stimulus-outcome associations, abstract visual stimuli (letters taken from the Agathodaimon font) will be utilized. Subjects will be told that they can earn a minimum of $40 for the scan session with up to an additional $40 depending on task performance.

During this session, participants will complete two measures of impulsivity outside of the scanner (Richards Delay Discounting Task and a short go/no-go task), a measure of working memory (Directed Forgetting Task), and a measure of selective attention (Dot-Probe Task). To incentivize participants to perform well, they will be told they can receive ten dollars if they perform in the top 25% of both tasks. Participants will also complete one clinical self-report measure (BDI-II) and two cognitive self-report measures: the Ruminative Responses Scale (RRS; Nolen-Hoeksema, 1991; the RRS is a 22-item self-report measure of ruminative cognitive style) and the Cognitive Style Questionnaire-Short Form (CSQ-SF; Meins et al., 2012; The CSQ-SF is an 18-item self-report of causal attributions for a list of negative hypothetical events). Participants will also complete the Young Mania Rating Scale to measure bipolar symptomatology.

Go/No-Go Task: the Go/No-Go Task is used as a measure of motor response inhibition. Participants are required to response to "Go" stimuli ("X", 85% probability) as quickly as they can by pressing a button with their right index finger, and to withhold a response to No-Go stimuli ("K", 15% probability). Response latencies, commission errors and omission errors are totaled to provide indices of motor response inhibition.

Directed Forgetting Task: The Directed Forgetting Task (Joormann & Gotlib, 2008) measures working memory in an emotional context. Participants are instructed to read a set of emotional words and hold the items in short-term memory; then discard ("forget") a subset of these words; and finally participants are presented with a word and must report whether or not the word was among the to-be-remembered items. This task is a measure of the ability to regulate the emotional contents of working memory, and takes approximately 20 minutes.

Dot-Probe Task: The Dot-Probe task (Joormann & Gotlib, 2007) is used as a measure of selective attention. Participants view a pair of images of emotional-expression faces appear on a computer monitor; after the faces disappear, a dot appears in the same location as one of the images, and the participant must respond as quickly as possible to identify the location of the dot. This task is a measure of the ability to ignore emotional faces, and takes approximately 10 minutes.

Mock Scan Procedure

Participants will have an opportunity to receive a "mock scan" that simulates the conditions of the actual scanner at the McLean Brain Imaging Center. In particular, participants will experience the sounds (i.e., repetitive metallic thumping), feel (i.e., enclosed within the scanner with head coil), and sights (i.e., will see what fMRI equipment looks like). During the process, participants will be trained to limit movement. Specifically, participants will be played a movie while they are in the mock scanner, and if there is too much movement, the movie will stop. Consequently, through repeated trial and error, participants will learn to reduce head movement, which may jeopardize the usability of scans. In addition to habituating to the scan environment, participants will also have an opportunity to ask questions about the process. Any and all questions will be addressed openly and honestly. It is expected that a mock scanner will be available at the McLean Imaging Center by the end of January.

Follow Up Interviews

Participants will be re-assessed at 3- and 6-month follow-up interviews, which will take place at the Center for Depression, Anxiety, and Stress Research at McLean Hospital. Information collected during these sessions will allow us to test the utility of our behavioral and neuroimaging measures in predicting subsequent symptom severity. Each follow-up time point will consist of an interview that will re-assess clinical measures previously administered during the behavioral session. This includes the IDS (Rush et al., 1996), SF-36 (McHorney et al.,1993), PSS (Cohen et al., 1983) ATRQ (Chandler et al., 2009), GHQ, MCQ, BISS (Bowden et al., 2007), BDI-II (Beck, et al., 1996); CGI-S and CGI-I (Guy, 1976), SF-36 (McHorney et al.,1993), Q-LES-Q (Endicott et al., 1993), MASQ (Watson et al., 1995), TEPS (Gard et al., 2007), ATRQ (Chandler et al., 2009), BIS (Patton, Stanford & Barratt, 1995), YMRS (Young et al., 1978); Richards Delay Discounting Task (Richards et al., 1999) as well as the Longitudinal Interval Follow-up Evaluation (LIFE; Keller et al., 1987; the LIFE assesses symptomatology, treatment intensity, and psychosocial functioning for naturalistic studies) The SCID will not be re-assessed as part of these sessions. Each follow-up interview session is expected to take approximately 2 hours.

Debriefing

At the conclusion of the study, subjects will be fully debriefed by a member of the study staff. (S)he will outline the purpose of the study and explain the purposes of the scans and tasks. The study staff member will explain the differential reinforcement schedule utilized in the probabilistic reward task. They will explain the partial contingency between the accuracy of the subject's choices and his/her likelihood of receiving positive feedback, and the rationale for use of this paradigm. The experimenter will also explain how results of the project might inform our understanding of the interactions between reward responsiveness and mood and how this may apply to classification of mood disorders. A copy of the debriefing form has been included as an attachment to this submission.

Participant Remuneration

For session one, subjects will be compensated for their time with $15 per hour and $15.80 for the PRT task. For the behavioral session (session 2), subjects will be compensated with $54 for completing the EEG, $16.20 for the PRT and $16.25 for the delay discounting task. For the neuroimaging session (session 3), subjects will be compensated with $40 for the scan session, an additional $40 for the reward learning task, an additional $10 in cash for the Dot-Probe and Directed Forgetting tasks, as well as $15 in cash for completion of the full session. Subjects will be compensated with $50 for each follow-up interview (3- and 6-month). Participants will be also reimbursed for transportation costs ($25/session) for sessions two and three, as well as the follow-up interviews. Lastly, if participants complete only part of a study session, they will be compensated in a prorated manner, such that if they complete half of a study session, they will be compensated half of the total amount for that session. If the participant completes all of the sessions, they can earn up to $352.25.

b. Drugs to be used

Not applicable

c. Devices to be used

Not applicable

d. Surgical interventions

Not applicable

e. Data to be collected

Please see below for details on data collected and analyses performed.

VI. BIOSTATISTICAL ANALYSIS

a. Specific data variables being collected

EEG. 128-channel EEG will be recoded using the Geodesic Sensor Net system (EGI, Oregon). EEG recording will take place in an electrically and acoustically shielded room in Dr. Pizzagalli's laboratory. Data reduction and analyses for ERP will follow our published work (Santesso et al., 2008).

fMRI/MRI. MRS/MRI data will be acquired at McLean Imaging Center on a 3T Siemens magnet with a 32-channel headcoil. Collection of structural data and resting fMRI data includes: a 13-s localizer scan; an "auto-align scout" scan that uses a reference database to ensure consistent slice positioning across subjects; a rapidly acquired (~2 min), T1-weighted, multi-echo MPRAGE volume for structural analysis and localization of fMRI data (1.2 mm isotropic voxels; TR = 2.2 s; flip angle = 7 deg; TE1 = 1.54 ms; TE2 = 3.36 ms; TE3 = 5.18 ms; TE4 = 7.01 ms; 144 slices); a T2-weighted structural volume for multispectral morphometry; and a T2*-weighted series sensitive to BOLD contrast for task-evoked fMRI data.

fMRI data will be analyzed using a linear regression model. Each trial will be modeled as having two time points (stimulus and outcome). Each stimulus condition and outcome will be modeled separately. Prediction errors generated by a Q learning model will be used as parametric modulation of regressors (Pessiglione et al 2006). This will be achieved by fitting a standard reinforcement learning algorithm (Sutton and Barto 1998) to each subject's sequence of choices. Based on individual choices and outcomes, for each pair of stimuli A and B, the basic Q learning algorithm will compute the expected values of choosing A (Q_a) and choosing B (Q_b) (Frank et al., 2007; O'Doherty et al., 2004). This value is the expected reward obtained by making that

particular choice. At the beginning of the task, these Q values are set to zero; after every trial *t,* the value of the chosen stimulus (e.g., A) will be updated according to the rule $Q_a(t+1)=Q_a(t)+\alpha*\delta(t)$, where $\delta(t)$ is the prediction error [$\delta(t)=R(t)-Q_a(t)$], i.e., the difference between the expected outcome [Q(t)] and the actual outcome [R(t)]. The reinforcement magnitude R will be +1 and -1 for winning and losing $1, respectively, and 0 for neutral outcomes. Based on the Q values, the probability of selecting an action will be computed using the softmax rule (Luce, 2003). Next, regressors will be convolved with a canonical hemodynamic response function. Linear contrasts of regression coefficients will be computed at the individual subject level and then taken to a group level random effects analysis. Using linear contrasts, main analyses will investigate representation of prediction errors as well as responses to the stimuli. ROI analyses will be performed with a focus on striatal and prefrontal regions reviewed in Section A.2, followed by whole-brain analyses. Whole-brain data will be thresholded at voxelwise $p < 0.005$ and corrected for multiple comparisons using Gaussian Random Fields. Only clusters significant at $p < 0.05$ (corrected) will be interpreted.

MRS. The acquisition protocol described in a preliminary test-retest reliability MRS 3T study, which has been extensively used at McLean Hospital (e.g., Henry et al., 2011; Jensen et al., 2009; Ongur et al 2008), will be implemented. Using high-resolution, T1-weighted MPRAGE anatomical images, a 2x2x2 cm voxel will be place over the each subject's rostral anterior cingulated cortex (rACC). The voxel will be shimmed using Siemens' automated shimming routine and the tip-angle, water-suppression, frequency and coil-tuning will be automatically adjusted. A 2D-JPRESS sequence will be used to collect 22 TE-stepped spectra with: TE: 35-350ms (15ms increments, f1 bandwidth: 67Hz); TR: 2s; spectral bandwidth: 1.2 kHz; readout: 512 ms. The resulting 2D-JPRESS spectra will be fitted using LCModel templates. These procedures have shown excellent test-retest reliability (Brennan et al 2010; Jensen et al 2009; Ongur et al 2008). Because MRS cannot distinguish neuronal from non-neuronal sources of Glu, the ratio of Gln to Glu provides the best index of overall glutamatergic transmission. The Gln/Glu ratio within this voxel will be the primary MRS measure of interest.

Behavioral Data: For the PRT, the main dependent variable will be Reward Learning, as operationalized as the increase in response bias during the final block relative to the first block [= DResponse Bias = Response Bias(Block 3) - Response Bias(Block 1)]. This variable was selected because it has been repeatedly linked to current and future anhedonic symptoms (Pizzagalli et al., 2005, 2008b; Vrieze et al., 2013a).

b. Study endpoints

Not applicable

c. Statistical methods

Data analyses will proceed in two stages. First, descriptive statistics and graphs will be used to assess the presence of skewness and/or outliers in the four main variables of interest (*Aim 1*). Continuous/quantitative variables will be appropriately transformed. Similarly, covariates in regression analyses (*Aims 1 & 2*) will be summarized to determine whether a continuous versus categorical representation is the most appropriate. For these regressions, the analytic approach will address the type of outcome (e.g., continuous or discrete) and the functional relationship between covariates and outcome (e.g., linear versus non-linear). The second stage will involve the analyses of the central hypotheses in *Aims 1-2*:

Aim 1: For Hypothesis 1, we will first use multiple regression to examine the relationships between our behavioral and neuroimaging measures and the symptom domains of anhedonia, mania and impulsivity, which will be assessed using the symptom severity collected during session 2. Standard multiple regression techniques will be used to identify the optimal weights for each unit of analysis (MRS, fMRI striatal PE signals, ERP FRN, PRT response bias). Additionally, to take advantage of the correlations between the three symptom domains and to potentially improve predictive accuracy, a single multivariate analysis (canonical correlation analysis) will be used to assess a separate set of weights reflecting the contribution of each unit in relationship to all three symptom domains simultaneously. For ease of interpretation, the latter analysis will be based on the first pair of canonical variables. Models will be fit using SAS PROC CANCORR.

Aim 2: For Hypothesis 2a, symptom inventories collected during follow-up interviews will be used to investigate incremental predictive validity of each unit of analysis in predicting subsequent symptoms while controlling for baseline severity. For these models, our behavioral and neuroimaging measures will be modeled using the relative weighting derived from the analyses described in aim 1. For quantitative measures (e.g., depressive and anhedonic symptoms), linear mixed effects models will be used. These models incorporate random subject effects to account for correlation among the repeated outcome measures (months 0, 3, 6); models will be fit using SAS PROC MIXED. Hypotheses concerning frequency measures (e.g., frequency of impulsive/risky behaviors) will be tested in a similar way. Models will be fit using SAS PROC GENMOD. Statistical tests and confidence intervals will be based on the "sandwich" estimator of standard errors to ensure that correlation among repeated assessments and overdispersion is accounted for.

d. Power analysis

Sample size and power calculations

Sample size determination was calculated based on observed effect sizes derived from prior studies that in our lab. Effect sizes were calculated using a = 0.05 (two-tailed) for (1) detecting relationships between reward learning variables across different unit of analyses and reward-related symptoms (e.g., anhedonia, mania); and (2) to predict symptom severity measures in a naturalistic follow-up study. Based on these estimates and allowing for 15% patient attrition or data loss, the sample will be: 80 treatment-seeking individuals with mood disorders recruited from three clinics as well as 32 psychiatrically healthy controls.

For group comparisons, multiple past studies using the PRT have found that unmedicated MDD subjects exhibited reduced reward learning compared to controls (Cohen's d: -0.70; Pizzagalli et al 2008c; Cohen's d: -0.61; Vrieze et al 2013a). In contrast, euthymic individuals with bipolar disorder had significantly higher reward learning relative to controls (Cohen's d: 0.72) (Pizzagalli et al 2008b). For the reinforcement learning task proposed for our fMRI study (Pessiglione et al 2006), we found that, relative to healthy controls, MDD subjects had significantly lower accuracy during reward learning (Cohen's d: -1.54). These effect sizes translate to power >0.98 for detecting group differences with the proposed sample size. For dimensional approaches, past studies have shown a strong large effect for the relationship between reward learning and anhedonic symptoms in BPD patients (r = -0.59). Moreover, among healthy subjects, reward learning predicted anhedonic symptoms 30-40 days later (r = -0.41, $p<0.05$). In light of these effect sizes, a total of 80 individuals with mood disorders leads to a power of >0.97 of (1) detecting relationships between units of analysis and reward-related symptoms (e.g., anhedonia, mania), and (2) predicting clinical outcome in the naturalistic follow-

up study. Finally, in an fMRI study probing reward processing, unmedicated MDD subjects showed weaker activation than controls to gains in the caudate (d = -0.98) and left Nac (d = -0.73) and left putamen (d = -0.78) during reward anticipation (Pizzagalli et al 2009), yielding a mean effect size of -0.87. In light of an average ES of 0.83 in the fMRI study, a total of 80 individuals with mood disorders and 32 healthy controls leads to a power >0.97 of detecting group differences.

VII. RISKS AND DISCOMFORTS

The risks associated with participation in this study are minimal, and every possible precaution is being taken to further reduce potential risks, as described below:

Behavioral component. We foresee no risks from the behavioral tasks required for the proposed research.

Genetic component.

No risks are expected from the saliva collection, from which DNA will be extracted. No additional risks are associated with participation in this component of the study. The major concern in this or any genetic study is patient confidentiality. In this case, study staff will at no time have access to the code keys required to match patient identifiers to patient names. Confidentiality of all subjects will be protected per institutional and NIH requirements. To protect confidentiality, saliva samples and genetic information will be stored in research files identified only by code. The code key connecting IDs to identifying information will be kept in a separate secure location. Data in databases are similarly identified only by coded ID number and are password-protected. Data will not leave our institution in any form that would identify individual subjects or their families. The results of genetic analyses will be kept confidential and will not be returned to participants in this study. Consequently, the potential risks of subjects' learning potentially sensitive genetic information or of discrimination related to participation in a genetic study should be avoided. The following steps will be taken to protect the confidentiality and privacy of the genetic data:

a) No genetic research data will be entered into the medical record.

b) The results of the genetic analyses will not be shared with participants or their family members.

c) Data will be encoded using coded identifiers. These codes, rather than personal identifiers, will be used in any analytic datasets. The code key linking identifiers to personal identifiers will be kept in an access-restricted, password protected electronic file. Any hard copies of such links will be kept in one of our locked research offices. Only the PI and authorized study staff will have access to these links.

EEG. We foresee only minimal risks from the EEG recording, a commonly and widespread procedure used to non-invasively measure electrical brain activity. The EEG will be recorded with the Geodesics Sensors Net, which requires no scalp abrasion. On rare occasions, individuals with very sensitive skin may experience a slight irritation at the site of sensor application due to the use of mildly salinated water.

fMRI

Implants/Prostheses: The magnetic field of the scanner exerts a force on ferromagnetic objects within the field. This force can cause a ferromagnetic implant, such as some brands of aneurysm

clips, surgical clips, or prostheses, to move or be displaced and cause injury or death. If the implant is both large and ferromagnetic, sufficient currents can be induced in the metal by the magnetic field to cause heating of the implant. *Individuals with any such devices will be excluded from enrolling in the study.*

Pregnancy: The safety of the 3.0T MRI scanner for imaging embryos/fetuses has not been clearly established. *Therefore, pregnant women or women of childbearing potential who 1) have not completed a negative urine pregnancy test prior to the MRI scan and/or 2) are seeking to become pregnant or believe that they may be pregnant, will be excluded.*

Collision Hazard: The magnetic field near the scanner is strong enough to attract ferromagnetic objects with great force. Near the magnet this force can be strong enough to pull objects in and cause them to fly down the axis of the magnet. Such objects become projectiles that can cause injury or death. A security zone has been established to prevent ferromagnetic objects from coming into proximity of the magnet. The likelihood of a collision in the context of the present experiment is thought to be low, much lower than the likelihood in clinical practice.

RF and Magnetic Field Interference: Implants electronic devices, such as cardiac pacemakers and cochlear implants, may be susceptible to interference from the magnetic and RF fields produced by the scanner. This interference may destroy or adversely affect operation of these devices. Since interference to cardiac pacemakers is observed in magnetic fields as low as 13 gauss, means have been provided to prevent persons with cardiac pacemakers or other implanted electronic devices from entering a zone where the magnetic field exceeds 5 gauss. *Individuals with such devices will be excluded from the study.*

Biomagnetic Hazards: It is possible that subtle genetic or molecular changes could be caused by the magnetic fields produced by the MR system. To date, however, no harmful biological effects have been demonstrated at the magnetic field strengths and exposure times utilized by the scanner. At the present time, the likelihood of any significant adverse biomagnetic effect is considered to be very low.

Neurostimulation: Some subjects undergoing functional MRI have experienced minor neurostimulation effects, such as muscle twitches and "tingling" sensations, due to the rapidly oscillating magnetic field gradients used in these examinations. There are no known risks associated with these effects. Specifically, the potential for cardiac stimulation has been examined and judged not to be a problem. The devices used in our research create field gradients that are within the limits specified by the FDA. Likewise, the head resonator for the McLean 3.0T scanner operates within FDA guidelines.

Clinical Hazards: The confining conditions of the MR system can precipitate claustrophobia in a subject. *Subjects will be screened for possible claustrophobia before they are enrolled in the study.*

Access to MR Area: Access to all areas exceeding the 5 gauss level will be controlled by warning signs, barriers, staffed entry locations, and adequate interrogation to assure avoidance of incidents. Access to the magnet room by any personnel will be closely controlled for safety of persons, in particular to prevent accidental introduction of ferromagnetic objects that could be attracted by the magnetic field generated by the MR system.

Device complications/malfunctions Not applicable.

Psychosocial (non-medical) risks

Suicidal Ideation and Imminent Harm. Any suicide threat will be taken seriously, and risk for suicide will be assessed via diagnostic interview and self-report data. If an individual endorses suicidal ideation on the online recruitment survey by entering a 1 or above on item 9 of the Beck Depression Inventory, he/she will have a link displayed on the webpage to a PDF of Community Resources. Additionally, if an online recruitment respondent enters a 2 or above on this item, a member of the research staff will phone him/her and follow the protocol outlined in the lab policy for suicidality. Moreover, study staff will assess every subject at each visit for suicide risk and potential. Subjects will be excluded from the study if they present as an imminent suicide risk (determined by the clinical interviewer), or report a history of serious suicidal behavior. The presence of serious suicidal behavior will be defined (using Columbia-Suicide Severity Rating Scale criteria) as either (1) one or more actual suicide attempts in the three years before study entry with the lethality rated at three or higher, or (2) one or more interrupted suicide attempts with a potential lethality judged to result in serious injury or death. A psychiatrist on call 24 hours a day will cover emergencies that may arise during one of the behavioral or imaging sessions. Individuals who present as elevated suicide risks will be treated appropriately, including psychiatric hospitalization. Our lab has significant experience working with this patient population, and has instituted a lab-wide protocol for addressing suicidal ideation. A copy of this protocol has been appended to this submission.

Plans for dealing with severely depressed individuals, suicidality, mania and referral for psychiatric treatment. Patient subjects referred to this study will have been pre-screened by study staff of these clinics to ensure that participation is appropriate. In addition, a full psychiatric interview will be conducted during the Behavioral/EEG testing session for both patients and healthy control subjects. In the unlikely event that a diagnosis of current severe depression or current manic episode is made when the SCID is administered, the clinical interviewer (research psychiatrist, licensed psychologist, or trained clinical research coordinator) will make a further assessment of current suicidal intent and planning, and/or severity of manic symptoms. If the clinical interviewer judges that the subject is in imminent risk of self-harm, she will walk the subject to MGH's Acute Psychiatry Service (APS) or the McLean Hospital Clinical Evaluation Center (depending on where the clinical assessment session takes place), both of which provide emergency psychiatric care on a 24/7 basis. The Clinical Evaluation Center is located on the McLean campus (3-min walking distance from the PI's laboratory) and specializes in the assessment and stabilization of individuals undergoing an acute psychiatric crisis. The PI will immediately be informed should this situation arise. If the participant refuses to comply with this plan, we will call the 24-hour MGH or McLean Crisis Mental Health Care services for immediate assistance and evaluation concerning possible hospitalization, and we will inform the staff of the subject's location and risk level. Under no circumstances will a participant expressing imminent suicidality be allowed to leave an interview or experimental session unattended. Furthermore, all steps taken to assess suicidality and ensure participant safety will be documented and submitted to the IRB for review. Note that the steps outlined above are to be followed when there is an imminent risk of suicide, due to a high level of suicidal intent and/or a specific plan of action; similarly structured but less involved plans are also in place when low, moderate, or high levels of risk are uncovered. For example, if risk is judged to be moderate, the project protocol calls for the interviewer, in consultation with the PI, to provide crisis phone numbers as well as relevant referrals for therapy, and to verify that the subject understands how best to access these resources.

Radiation risks
Not applicable

VIII. POTENTIAL BENEFITS

Potential benefits to subjects:
There will be no direct benefits to the subjects for participating in this research other than the knowledge they may gain about scientific research methods. Subjects will be compensated for their time with $15 per hour for the screening session and $15.80 for the PRT, $54 for the EEG session with $16.20 for the second PRT and $16.25 for the delay discounting task, and $40 for the MRI session with $40 for the reward learning task, $10 for the Directed Forgetting and Dot-Probe tasks, and $15 for completing the entire session. Subjects are also reimbursed $50 for each follow-up (3- and 6-month). Participants will be also reimbursed for transportation costs ($25/session). Lastly, if participants complete only part of a study session, they will be compensated in a prorated manner, such that if they complete half of a study session, they will be compensated half of the total amount for that session. If the participant completes all of the sessions, they can earn up to $352.25.

Potential benefits to society:

The ultimate aim of this project is to improve our understanding of the pathophysiology of a wide range of mood spectrum disorders, with a particular focus on brain mechanisms implicated in reward processing. By integrating several levels of analysis while studying healthy subjects and individuals with unipolar or bipolar depression of varying severity, this project will furnish a rich dataset on the neurobiology of human reward learning. The expectation is that this dataset will provide insight into pathophysiological mechanisms that are transdiagnostic and that can ultimately be targeted for treatment. Given the magnitude of human and economic costs associated with depression, the important opportunity to begin linking basic neuroscience research with applied clinical concerns, and the minimal risk involved in study participation, we believe that the risks to subjects are reasonable relative to the benefits of this work.

IX. MONITORING AND QUALITY ASSURANCE

a. Independent monitoring of source data
Not applicable.

b. Protection against risk/Safety monitoring
Every effort will be made to reduce subjects' anxiety about study procedures. Research interviews and experimental assessments will be interrupted if participants become distressed, and subjects will be carefully monitored by laboratory staff during all aspects of the project. Specific protocols for assessing and handling suicide risk factors and suicidality are described above. Finally, if any adverse event occurs during the imaging protocols, appropriate medical intervention will be provided: a physician will be on call for the MRS/MRI scans and EEG/behavioral session.

Confidentiality will be maintained throughout the project period. Subject names will not appear on data records, and a standardized code will be used to label each subject's data. Results of diagnostic interviews will be coded and stored in locked filing cabinets. Similarly, behavioral, EEG, and MRS/MRI data will be coded and stored on password-protected computers. The key

linking ID codes to identifying information will be kept in a locked filing cabinet or password-protected computer, and will be separate from the data. Data will not leave McLean Hospital in any form that could result in identification of subjects or their family.

Adverse Events reporting

1) Serious adverse events that are reportable according to the guidelines of the Office for Human Research Protections (OHRP) and FDA (e.g., death, suicide attempt, inpatient hospitalization) will be reported to the Partners IRB, McLean Hospital IRB, and the NIMH program officer. A full written report will be sent to these entities. Adverse events and unanticipated problems involving risks to subjects or others will be reported to the IRB per PHRC reporting guidelines. Should a patient become ill or injured as a direct result of participation in this research, necessary medical care will be made available.

2) Any other unanticipated problems will be reported to the IRBs within two weeks, in accordance with OHRP and FDA guidelines.

3) All adverse events will be summarized in the NIMH and IRB annual progress reports.

4) We will inform the NIMH of any actions taken by the IRBs as a result of the continuing review of the proposed research.

Outcome Monitoring

Not applicable.

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