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PROTOCOL TITLE:
Pilot Study of Neuromodulation for Enhancement of Emotion Regulation in Bipolar Mood Disorders

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I. BACKGROUND AND SIGNIFICANCE:

Emotion dysregulation contributes to the development and maintenance of a wide range of psychopathology, but is especially relevant for individuals with bipolar mood disorders (BD). These individuals experience severe and episodic emotion dysregulation associated with maladaptive functioning, interpersonal problems, decreased work productivity, and suicidal ideation and behavior.[1-5] To date, both pharmacological and psychosocial treatments fail to normalize emotion dysregulation for many bipolar patients.[6-11] As a consequence, all too many experience poor outcomes. Thus, there is a significant need for new innovative approaches to target and improve emotion dysregulation in bipolar patients. Non-invasive neuromodulation using transcranial magnetic stimulation (TMS) may provide a viable strategy to help improve emotion dysregulation in bipolar mood disorders. As a first step to test this hypothesis, the current proposal seeks to experimentally identify specific neural target sites for improving emotion regulation using TMS. If we can demonstrate target engagement of emotion regulation at the behavioral level using TMS, this will provide an important first step towards examining the potential utility of TMS as a viable strategy to help improve emotion dysregulation in bipolar mood disorders. While this is not a definitive clinical trial, the sham-controlled double-crossover design of this study will provide valuable information for target site selection for the development of TMS as an intervention strategy to improve emotion dysregulation in BD.

Emotion dysregulation in bipolar mood disorders

Individuals struggling with bipolar mood disorders (BD) experience chronic emotion dysregulation that can permeate every aspect of functioning. The inability to adaptively regulate emotions leads to impulsive, risky or self-destructive behaviors; interpersonal problems; disruptions in work productivity; even suicidality.[1-5] Whereas our current pharmacological treatments oftentimes excel in maintaining overall mood stability, they nevertheless fall short of specifically targeting and ameliorating emotion dysregulation in many patients with BD.[8-10] Similarly, cognitive behavioral (CBT) and other psychosocial treatments fail to improve emotion dysregulation in more severely dysregulated patients, whose level of dysregulation ironically interferes with the ability to follow the highly didactic nature of these approaches.[1,7, 11, 12] Thus, there is a significant need for innovative approaches to address the problem of emotion dysregulation in BD.

What is emotion regulation?

Emotion regulation has been operationally defined as the process by which individuals influence and modulate which emotions they have, when they have them, and how they experience and express them.[13] In behavioral terms, this can be interpreted as the ability to enhance or inhibit automatic, emotion-driven behavioral responses given current contextual demands, so as to utilize affective information in the most optimal, adaptive manner. In neural terms, this translates to the reliable recruitment of neural structures to integrate emotionally salient information with goal-relevant information, and to regulate neural responses accordingly. Emotion regulation encompasses both implicit and explicit regulation processes.[14] Implicit emotion regulation refers to automatic, reflexive regulation of emotions, such as averting one's gaze when confronted with a distressing stimulus so as to dampen feelings of distress. By contrast, explicit emotion regulation refers to effortful, conscious regulation of emotions, such as deliberately ascribing a new, less distressing meaning to a distressing situation (e.g. cognitive reappraisal). Both forms of emotion regulation are important for healthy, adaptive functioning.

Targets for improving emotion regulation

If we think of emotion dysregulation in behavioral terms, there are identifiable behavioral or symptom-based targets for improvement with both pharmacological and CBT interventions. For example, teaching

emotion regulation skills like cognitive reappraisal through CBT, or dampening the interference of emotion intensity through medications. However, these interventions assume a baseline integrity of neural functioning exists that would enable the *capacity* for successful treatment. A major roadblock to successful treatment in BD lies in overcoming the very pathology these interventions are attempting to ameliorate. In concrete terms, patients with BD show deficits in emotion regulation at both behavioral *and* neural levels of examination, which limit the efficacy of existing treatments. Thus, there is a need to: 1) understand the neural pathophysiology associated with severe emotion dysregulation in BD; and 2) develop strategies to remediate and rehabilitate neural deficits to improve the capacity for adaptive emotion regulation.

What are the neural circuits supporting mechanisms of emotion regulation?

Existing studies of healthy individuals implicate a distributed neurocircuitry supporting both implicit and explicit emotion regulation. Specifically, converging evidence shows the ventrolateral prefrontal cortex (VLPFC), medial PFC (mPFC), anterior cingulate cortex (ACC), anterior insula and amygdala form a distributed network supporting adaptive emotion regulation.[15-17] Within this circuitry, amygdala and anterior insula serve to signal salience and sensory information,[16] whereas the VLPFC, ACC, and mPFC integrate and regulate this information according to cognitive or situational demands.[18, 19] The right VLPFC in particular, in conjunction with the anterior insula, has been shown to form a fronto-insular network that is crucial for adaptively switching between salience and executive control network processing, and plays a key role in regulating the intensity of emotional responses.[20] Increased VLPFC activation coupled with decreased amygdala activation has been found in studies of emotion regulation,[21] motivation and behavioral inhibition,[22] suggesting the VLPFC plays a particularly key role in maintaining emotional homeostasis for healthy, adaptive functioning. Additionally, unlike the dorsolateral PFC (DLPFC), the VLPFC has direct efferent anatomical connections to the amygdala, and afferent connections from the amygdala through anterior insula, as well as connections to dorsal and medial PFC, situating this structure in a key position to integrate emotional and cognitive information and affect plasticity along this distributed neurocircuitry.[15] Studies of both implicit *and* explicit emotion regulation have identified the VLPFC as playing a pivotal role in successful regulation.[21, 23]

Evidence for a reduced neural capacity for emotion regulation in bipolar disorder

Neuroimaging studies of individuals with BD consistently point to hypoactivation of bilateral VLPFC coupled with hyperactivation of limbic structures in the context of emotion processing, as well as aberrant amygdala-VLPFC functional connectivity.[24-31] For example, relative to healthy controls, decreased VLPFC activation and corresponding increased amygdala activation has been demonstrated during emotion regulation using cognitive reappraisal in euthymic BD patients.[26] Decreased VLPFC activation, and corresponding increased amygdala activation, has also been demonstrated during performance on emotional Stroop and affect labeling tasks.[25, 28, 32, 33] Several studies have shown increased functional connectivity between amygdala and VLPFC during emotion regulation and at rest, suggesting inefficient downregulation of amygdala by VLPFC.[29, 30] This suggests euthymic BD is associated with a functional disruption in a key neural pathway by which the VLPFC exerts regulatory control over amygdala responses. Thus, impaired recruitment of VLPFC and disrupted functional connectivity between VLPFC and the broader neurocircuitry supporting emotion regulation may play a key role in the severe emotion dysregulation seen in bipolar disorder.

Evidence for additional potential target sites for neuromodulation

Using data from our lab, we have evaluated the baseline integrity of emotion regulation circuitry in BD by examining resting state functional connectivity of the insula to key regions of interest in executive control, default mode, and salience processing functional networks.[34] BD patients were distinguished from healthy controls by weaker right anterior insula-right VLPFC functional connectivity (p=.04), replicating existing studies discussed above. However, a stronger finding from this study showed significantly weaker right anterior insula functional connectivity to the left inferior parietal lobule (IPL) distinguished BD patients from both HCs and patients with unipolar depression (HC>BD: p<.001; MDD>BD: p=.01; Fig 1). Further, using a receiver-operator characteristic analysis, we found anterior insula-IPL functional connectivity exhibited moderate to good specificity, sensitivity, and negative predictive value in classifying bipolar patients from unipolar or healthy controls. IPL functional connectivity was significantly correlated with self-report measures of perceived affective control, such that stronger IPL-insula functional connectivity predicted greater perceived control. As a key node in the fronto-parietal executive control network, the IPL has been shown to play a major role in emotion-cognition integration and regulation, and is an important regional hub within an integrative multi-network system implicated in orienting attention and regulating cognitive resources in response to salient stimuli.[35-37] The IPL also shares strong functional connections to anterior insula, VLPFC, and dmPFC regions of the salience network, and is strongly activated in tasks requiring simultaneous processing of interoceptive or affective cues and cognitive demands.[38, 39] Thus, both the VLPFC and the IPL may be candidate target sites for improving emotion dysregulation in BD.

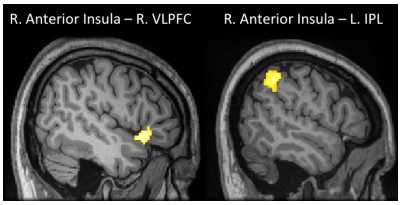


Fig. 1 Insula connectivity, HC>BD (Ellard et al., in press, Biol Psych: CNNI).

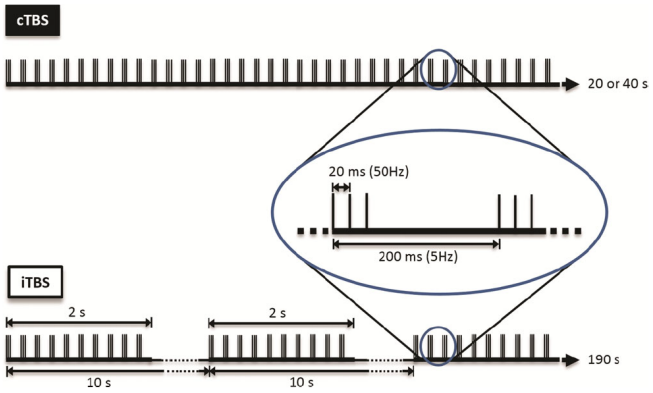
Why use TMS?

Transcranial magnetic stimulation (TMS) is a noninvasive and well-tolerated method of neuromodulation in which magnetic fields applied over the surface of the skull generate electrical currents to stimulate or inhibit targeted brain regions[40]. TMS has a well-established safety profile and it is able modulate brain activity without surgery, anesthesia or the generation of a convulsion[41]. Single and paired-pulse TMS protocols have been used since the mid-1980s to study human neurophysiology, with a focus on the motor system, cortical excitability and neuroplasticity[42]. Diagnostic applications have been FDA-approved for years, allowing the use of these protocols by clinical neurophysiologist for the assessment of pathologies affecting the pyramidal tract (i.e. motor conduction studies)[43]. Repetitive TMS (rTMS) refers to the application of multiple pulses of TMS, repeated over the course of a given session, with frequencies commonly varying between 1Hz and 50Hz[40]. Repetitive TMS has been used extensively in systems and cognitive neuroscience research, given its capacity to modulate (both up- and down-regulating) brain regions and networks. Importantly, the safe and well-tolerated yet interventional nature of TMS has allowed the establishment of causal relationships between brain activity and mental states in humans in vivo (e.g.,[44]), something that other observational noninvasive neuroscience tools (e.g., neuroimaging) are unable to do (these are limited to establishing correlations). Repetitive TMS (rTMS) has been suggested to induce changes in neural activity at the systems level, which may contribute to its therapeutic effects. In the motor cortex, high frequency rTMS (hf-rTMS) has been shown to increase cortical excitability, while low frequency rTMS (lf-rTMS) has been shown to decrease excitability[45]. Clinically, rTMS has been FDA approved for therapeutic indications and since 2008 it is used for the treatment of major depressive disorders[46, 47]. Of primary relevance to this study, TMS has been safely administered to the cerebellum in wide-ranging studies focusing on saccadic eye movements[48-50], spinocerebellar degeneration[51], visual motion processing[52], timing tasks[53, 54], ataxia[55, 56], motor learning[57], Parkinson's disease[58, 59], and SZ[60].

Theta burst stimulation (TBS) is a very efficient rTMS protocol that uses high frequency rTMS burst with lower stimulus intensity, smaller number of pulses and much shorter train duration, yet capable of facilitating longer-lasting post stimulation effects compared with traditional rTMS[61, 62]. TBS was

developed in 2004, based on the physiologic pattern of neuronal firing found in the hippocampus of animal[61]. The basic element of TBS contains a three-pulse burst at 50 Hz given every 200 milliseconds (i.e. at 5 Hz). By using this basic pattern, two major TBS paradigms were developed: continuous theta burst stimulation (cTBS, inhibitory) and intermittent theta burst stimulation (iTBS, excitatory), as shown in Figure 2. The stimulus intensity required for TBS (80% of active motor threshold –AMT) is lower than that for traditional rTMS protocols, which use 100 to 120% of the resting motor threshold (RMT). Of note, not only the percentage is less, but the AMT is also of lower intensity than the RMT. Consecutive sessions of TBS have been safely administered in SZ[60, 63-65] and in BP[66-69].

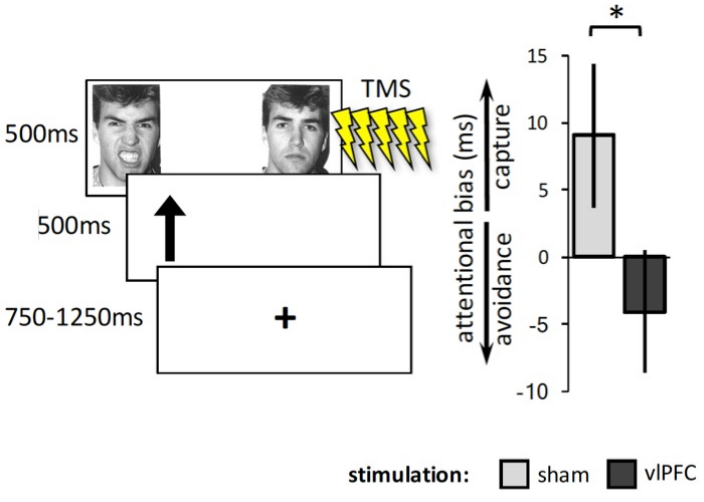
Figure 2: Continuous and Intermittent TBS protocols (from Chung et al., 2015)



In this study, we will administer iTBS-TMS to the right VLPFC, the left IPL, and sham (inactive) TMS to the right dorsomedial PFC (dmPFC), in order to study the relative effects of TMS applied to the VLPFC versus the IPL on performance on emotion regulation tasks. In this way, we can identify a viable treatment target to develop and test TMS as an intervention to improve emotion regulation in bipolar disorders.

Prior evidence for single session TMS-enhanced emotion regulation

Existing evidence suggests using single-session TMS to probe emotion regulation is a viable strategy. In a sample of healthy adults, De Raedt and colleagues[70] investigated the effects of a single session of high frequency (10 hz) repetitive TMS (HF-rTMS) over the left dorsolateral prefrontal cortex (DLPFC) on the ability to disengage from angry faces in order to identify the location of a probe. They found a single 20-minute session resulted in less engagement with angry faces and faster reaction time to probe location relative to sham TMS. Similarly, Etkin and colleagues (in prep) found applying single TMS pulses to the right VLPFC during an emotion dot probe task resulted in significantly less attentional bias towards angry faces and greater attentional regulation towards task-related goals (Figure 3). In a study investigating the effects of HF-rTMS on attentional control in depression, a single session of HF-rTMS over the DLPFC



resulted in significantly faster reaction times during a task switching paradigm relative to sham TMS.[71] Thus, prior evidence suggests single session rTMS is a viable strategy to modulate and improve emotion regulation and emotion processing in healthy and neuropsychiatric populations.

tion dot probe task. (Etkin et al., in prep.)

Why examine two target sites?
Prior studies indicate TMS can successfully engage VLPFC targets with subsequent regulatory effects. However, due to the anatomical location of VLPFC and the likelihood of stimulation-related muscular contraction (e.g. periocular, mandibular), concerns over tolerability and feasibility of this target site need to be considered (although prior studies have found discomfort to be negligible and stimulation at this site to be well tolerated, suggesting this may still be a feasible target for stimulation).[72, 73] Nevertheless, if we can demonstrate that stimulation to the IPL is at least as effective at improving emotion regulation behavior as stimulation to the VLPFC, the anatomical location of IPL may afford a viable TMS target with reduced risk for patient discomfort. Therefore, in order to identify a target site for the development of TMS as an intervention to improve emotion dysregulation in BD, the current study will evaluate the relative effectiveness of stimulation to these two target sites.

II. SPECIFIC AIMS

The specific aim of the present study is to examine the potential for targeted engagement of VLPFC versus IPL through iTBS-TMS to enhance emotion regulation performance in BD. Specifically, we propose to recruit 15 patients with BD and 15 healthy controls in a randomized cross-over design to receive excitatory iTBS-TMS to the right VLPFC, the left IPL, and sham (control) TMS to the right dmPFC. Before and after TMS, subjects will perform three well-validated emotion regulation tasks, one measuring explicit emotion regulation (i.e. cognitive reappraisal) and two measuring implicit emotion regulation (see below). Previous work in our group has demonstrated the feasibility of conducting similar TMS behavioral studies in patients with severe mood disorders and successful achievement of similar recruitment goals.

Specific Aim: To determine the relative effect of IPL versus VLPFC stimulation on emotion regulation circuit dynamics.

Hypothesis: We predict TMS to IPL will result in greater improvement in behavioral indices of emotion regulation (i.e. decreased reaction times during an implicit emotion regulation task, decreased ratings of distress on an explicit emotion regulation task) relative to TMS applied to VLPFC target sites, given the role of the IPL in top-down executive regulation of affective processes.

The current study will enable us to determine optimal target sites for intervention and inform future noninvasive and invasive rehabilitative interventions. The long-term goal of this project is to provide crucial target location data to support the development of noninvasive neuromodulatory approaches to improve emotion regulation in bipolar mood disorders.

III. SUBJECT SELECTION

We plan to enroll 20 patients diagnosed with bipolar I disorder for the study.

Inclusion Criteria:

- Men and women
- Ages 18-50 years
- Patients diagnosed with bipolar I disorder (BD-I), current mood state euthymic.

- On a stable psychiatric medication regimen for at least a month prior to and during study participation

Exclusion Criteria:

- Any change in psychiatric medications within a month prior to and during study participation
- Legal or mental incompetency
- Intellectual disability
- Current manic (YMRS > 12) or severe depressive episode (HAM-D-17 > 5)
- Substance use disorder (abuse or dependence) with active use within the last 3 months
- Significant medical or neurological illness
- Prior neurosurgical procedure
- History of seizures
- History of ECT treatment or clinical TMS within the past three months
- Implanted cardiac pacemakers
- Patients who have conductive, ferromagnetic or other magnetic-sensitive metals implanted in their head or neck, or are non-removable and within 30 cm of the treatment coil. These include:
  - Aneurysm clips or coils
  - Carotid or cerebral stents
  - Metallic devices implanted in the head (e.g. Implanted pacemaker, medication pump, vagal stimulator, deep brain stimulator, TENS unit, or ventriculo-peritoneal shunt)
  - Magnetically active dental implants
  - Cochlear/otologic implants
  - CSF shunts
  - Ferromagnetic ocular implants
  - Pellets, bullets, fragments less than 30 cm from the coil
  - Facial tattoos with metallic ink, permanent makeup less than 30 cm from the coil
  - Pregnancy; breastfeeding or nursing; for women of childbearing a pregnancy test (to be ruled out by urine β-HCG) will be conducted prior to study.

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Source of subjects and recruitment methods

Recruitment for the proposed study will take place through the Massachusetts General Hospital (MGH) Dauten Family Center for Bipolar Treatment Innovation (Dauten Center). The Dauten Center is a major research group at MGH, and includes 6 psychiatrists, 4 psychologists, 4 research coordinators, a full-time receptionist and support staff. Our clinic sees over 600 patients per year, and recruits on average 150 patients per year into research studies. The Dauten Center patient registry includes over 500 patients who have consented to be contacted for participation in research studies. Research studies are also advertised in a quarterly newsletter. In addition, the Dauten Center receives an average of 30 calls with requests for treatment per month, and callers are informed of existing opportunities to participate in research. Additional advertising for participation in the proposed study will be posted at the MGH Adult Outpatient Psychiatry Service.

We will recruit subjects who meet the eligibility criteria using approaches that are standard for intervention studies and that the Dauten Center have successfully used in previous clinical trials for bipolar disorder. Participants will be recruited via psychiatric referral through the Dauten Center and MGH Adult Outpatient Psychiatry Service. Additional recruitment will take place via advertisement through the Dauten Center Patient Registry and Partners Health Care as needed.

IV. SUBJECT ENROLLMENT

Screening for Eligibility

Potential participants will be pre-screened for study eligibility using a standardized form (see Healthy Control Phone Screen and Patient Phone Screen, attached). The form asks about age, medical and neurological illnesses, whether pregnant, psychiatric history, family history of psychiatric illness, substance use history, history of ECT or TMS treatments, history of participation in a TMS study, and any conditions that would preclude TMS administration (e.g., metal implants near the head or neck). If the potential subject cannot rule out the possibility of pregnancy, a pregnancy test will be conducted prior to study enrollment. In addition, patients will be screened for the presence of a current depressive or manic episode using the Quick Inventory of Depression Symptoms (QIDS) and the Altman Mania Rating Scale (AMRS). The screening interview will take approximately 10-15 minutes to complete.

Patient Screening: The research coordinator will be in contact with outpatient treaters within the Dauten Center for referrals about potential subjects. Patients who are interested will undergo a screening interview for inclusion and exclusion criteria either in person or by telephone. Patients who contact the Dauten Center and express interest in the study will undergo a screening interview by telephone.

Potential subjects will be informed that all information obtained during eligibility screening will remain confidential. Screening forms that are completed for individuals who end up not meeting eligibility criteria will be disposed of in the confidential waste bin for shredding, according to hospital guidelines.

Procedures of obtaining informed consent

Informed consent will be obtained on all study participants. All subjects who meet eligibility criteria will be given a description of the study, and any questions they may have will be answered. Participants must be capable of understanding the nature of this study, its potential risks, discomforts, and benefits. Since all participants will be 18 or older, they will provide consent without parental or other guidance. We will obtain informed consent after the study purpose and procedures have been fully and clearly explained, and the potential participant has demonstrated an understanding of the protocol, willingness to participate, and capacity to consent.

As a means of assessing participants' understanding of what the study entails, we will conduct a one-on-one informed consent survey, which asks questions such as, "What illness is being studied in this project?" "Are there any risks to participating in this study?" and "Will you lose any of your benefits if you refuse to participate in this study?" If the participant is unable to answer the questions or demonstrates a lack of understanding, the investigator will review the details of the study again. The survey therefore serves to ensure that participants are actively engaged in the informed consent process. For each participant, we will re-administer the informed consent survey at the beginning of each visit, in order to ensure that the participant is capable of consent throughout the entire study. Participants who are unable to answer all questions correctly even after additional information is provided will be excluded from the study.

We will acquire written informed consent for all participants using the IRB-approved consent form. All signed forms will be stored in a file cabinet in a locked office.

Treatment assignment, and randomization

All subjects, will receive all three iTBS-TMS interventions over the course of study participation. During each study visit, they will receive either excitatory iTBS-TMS to the right VLPFC, excitatory iTBS-TMS to the IPL, or Sham (inactive) TBS-TMS to the right dmPFC. The order in which they receive these iTBS-TMS interventions and the order of behavioral task presentation will be randomized for each subject by the study staff prior to the first TMS administration. Randomizations (TMS protocol, behavioral task order) will be conducted using software written by Gerard E. Dallal, Ph.D. of Tufts University (https://www.randomizer.org/). The investigators and the research coordinator will not be blinded to the randomized order, since all assessments pre- and post-TMS require input solely from the subjects. However, subjects will be blinded as to which mode of TMS they receive at each study visit. Sham TMS will use the exact same procedure with a sham coil, which is designed to induce the same nonspecific sensory effects of TMS (auditory and somatosensory activation) without inducing the neuromodulatory magnetic fields. At the end of each study visit, subjects will be asked to speculate on which mode of TMS (active or sham) they received as well as the degree of certainty of their judgment so that we can assess the potential contributions of subjects' expectations on their task performance.

V. STUDY PROCEDURES

All subjects, including healthy controls, will undergo three visits at the MGH Laboratory for Neuropsychiatry and Neuromodulation in the Charlestown Navy Yard Campus, with at least 36 hours separating the visits.

The subject is free to withdraw from the study at any time simply by informing the investigators. Similarly, the investigators may decide to stop the study if the purposes of the study cannot be met (technical difficulties, new information on subject characteristics, etc.).

Summary of Study Procedures
The first visit will include the following procedures (for the second and third visits, the clinical characterization step will be skipped):

- Consenting procedures (15-20 minutes)
- Clinical characterization (30 minutes):
    - Demographics Questionnaire
    - Young Mania Rating Scale (YMRS)
    - Hamilton Depression Rating Scale (HAMD-17)
    - Affective Control Scale (ACS)
    - Difficulties in Emotion Regulation Scale (DERS)
- Pregnancy screen if indicated (5 minutes)
- Baseline/pre-TMS behavioral computer tasks (30 minutes)
    - Multisource Interference – International Affective Picture Scale Task (MSIT-IAPS)
    - Emotion Conflict Resolution Task (ECR)
- Transcranial Magnetic Stimulation (TMS) (15 minutes)
    - Excitatory iTBS-TMS, VLPFC, IPL or sham dmPFC
- Post-TMS behavioral computer tasks (30 minutes)
    - Multisource Interference – International Affective Picture Scale Task (MSIT-IAPS)
    - Emotion Conflict Resolution Task (ECR)

Clinical characterization

For the purposes of clinical characterization, we will record demographic (i.e. age, sex, race/ethnicity, parental

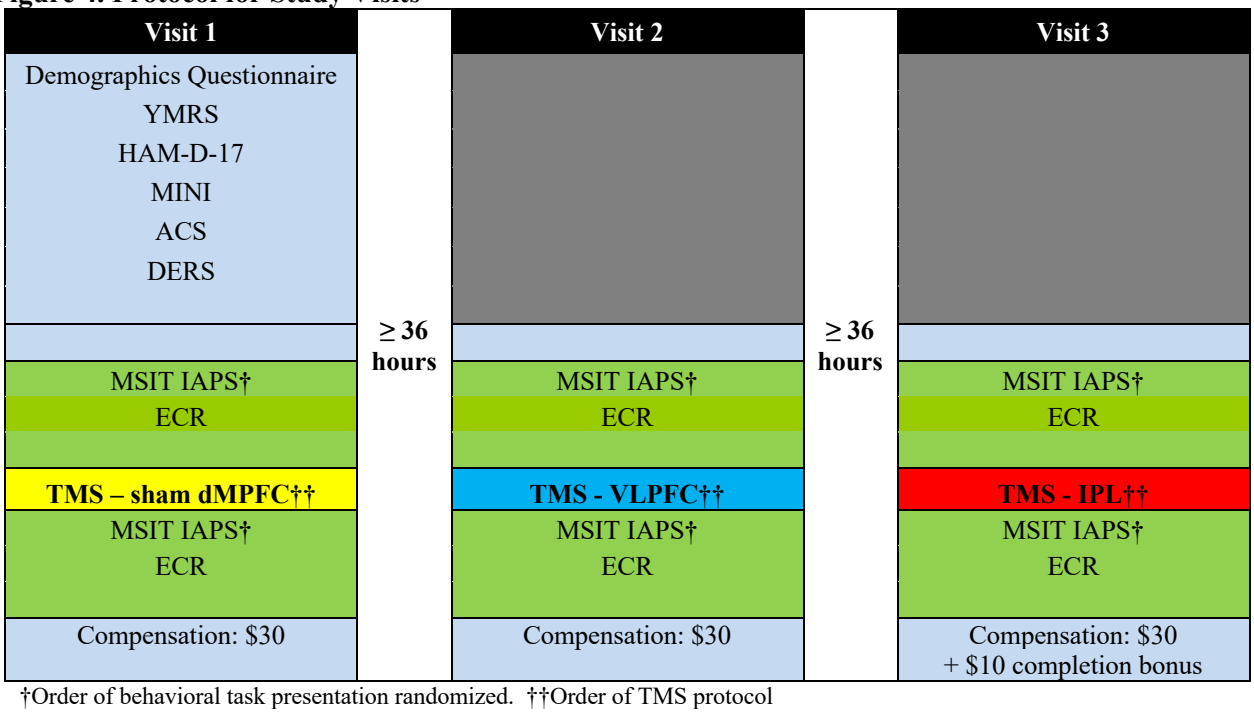
education, duration of illness, handedness) and medication information for all subjects during the first visit. For healthy control participants, we will administer the MINI, which assesses lifetime history of psychiatric symptoms and diagnoses, but not symptom severity, which can fluctuate over time. To capture the clinical presentation of patients at the time of the study, we will use the clinician-administered YMRS and HAM-D-17 to capture the most severe symptoms of mania and depression respectively in the previous month. The ACS and DERS, will be administered for all subjects to assess baseline emotion regulation skills. The clinical characterization step will not be repeated at study Visits 2 and 3.

Scheduling of study visits

This will be a cross-over design, in which participants will undergo excitatory iTBS-TMS to the VLPFC, excitatory iTBS-TMS to the IPL, or sham iTBS-TMS to the dmPFC over three study visits (Figure 4), separated by at least 36 hours. The order in which participants receive VLPFC vs. IPL vs. sham dmPFC TMS will be randomized.
The effects of a single session of rTMS are acute and reversible, and usually recede in less than an hour. Nonetheless, the study visits will be separated by at least 36 hours in order to provide more than ample time for the brain to return to homeostatic balance and ensure that there are no potential residual TMS effects from the previous study visit.

If scheduling permits, participants may be able to complete all three study visits in as short as one week. However, to accommodate scheduling flexibility for research participants, we will allow up to two months for participants to complete all three study visits within a single protocol.

Figure 4. Protocol for Study Visits



†Order of behavioral task presentation randomized. ††Order of TMS protocol randomized

Transcranial Magnetic Stimulation (TMS)

TMS has a well-established safety profile and it is able modulate brain activity without surgery, anesthesia or the generation of a convulsion (Rossi et al., 2009). Since its development in the mid-1980s, it has become a widely used tool for neuroscience research and for clinical applications, both diagnostic and therapeutic (Camprodon, 2014). Repetitive TMS (rTMS) has been suggested to induce changes in neural activity at the systems level, which may contribute to its therapeutic effects. In the motor cortex, high frequency rTMS (hf-rTMS) has been shown to increase cortical excitability, while low frequency rTMS (lf-rTMS) has been shown to decrease excitability (Maeda et al., 2000).

We will use a MagVenture MagPro X100 with MagOption stimulator and two dynamic cooled butterfly coils: one real and one sham (MagVenture, Denmark) navigated with an infrared TMS Neuronavigation Research Premium system (Localite, Germany) to administer the TMS.

We will start by measuring the patient´s motor threshold (MT), which is a measure of cortical excitability used to standardize the intensity of stimulation across subjects. To do this, the TMS coil is placed over the primary motor cortex (M1). Single pulses are applied with an interpulse interval (IPI) of at least 5 seconds, to prevent additive neuromodulatory effects. When pulses are applied at suprathreshold intensities, a volley of activity travels through the pyramidal motor pathways and leads to the contraction of the contralateral target muscle (generally the Abductor Pollicis Brevis, Fist Dorsal Interosseus or Tibialis Anterior). The intensity of stimulation is sequentially reduced until we reach a point when fewer than 50% of the pulses (usually <3 out of 6) lead to a muscle contraction (identified by visual inspection or neurophysiological motor evoked potentials). The first TMS intensity that is unable to elicit a muscle contraction more than 3 out of 6 pulses is considered the motor threshold, and usually expressed as a percentage of the maximum stimulator output.

Once the MT is determined, we will apply iTBS to our target site (VLPFC, IPL or dmPFC). Using the Localite TMS MR-less neuronavigation system and standardized regional masks, we will place the TMS coil over the scalp position that allows direct stimulation of the target region.

In a random order, patients will receive iTBS-TMS (excitatory) to VLPFC or IPL, or sham iTBS-TMS to the dmPFC, in each of the 3 sessions. Subjects will be blinded as to which mode of TMS (active versus sham) they receive at each study visit. Sham TMS will use the exact same procedure with a sham coil, which is designed to induce the same nonspecific sensory effects of TMS (auditory and somatosensory activation) without inducing the neuromodulatory magnetic fields. At the end of each study visit, subjects will be asked to speculate on which mode of TMS (active or sham) they received as well as the degree of certainty of their judgment so that we can assess the potential contributions of subjects' expectations on their task performance.

Assessment measures

1. *Affective Control Scale (ACS; Williams, Chambless, & Aherns, 1997)*. The ACS is a 42-item self-report measure designed to assess fear of loss of control when experiencing strong affective states. ACS subscales expand on the construct of fear of fear, including *fear of anxiety*, *fear of depression*, *fear of anger*, and *fear of strong positive affective states*. The ACS has demonstrated acceptable internal consistency, test-retest reliability, and concurrent and divergent validity (Berg, Shapiro, Chambless, & Aherns, 1998; Williams et al., 1997).

2. *Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004).* The DERS is a 36-item, self-report measure developed to assess clinically relevant difficulties in emotion regulation. The DERS is divided into six subscales assessing the following dimensions of emotion regulation: 1) nonacceptance of emotional responses (Nonacceptance); 2) difficulties engaging in goal-directed behaviors (Goals); 3)

impulse control difficulties (Impulse); 4) lack of emotional awareness (Awareness); 5) limited access to emotion regulation strategies (Strategies); and finally, 6) lack of emotional clarity (Clarity). The DERS has demonstrated excellent internal consistency and good test-retest reliability. The DERS subscales have demonstrated adequate internal consistency and adequate test-retest reliability (Gratz & Roemer, 2004).

3. *Hamilton Depression Rating Scale (HAM-D-17; Hamilton, 1960).* Clinician-rated depressive symptoms were assessed monthly using 17-item HAM-D-17. The HAM-D-17 is a well-established clinician-rated structured interview with high reliability and validity, recently re-evaluated in a large meta-analysis [74].

4. *Mini Neuropsychiatric Interview (MINI; Sheehan et al., 1992).* The MINI is a brief diagnostic assessment measure developed to screen for the presence of current and lifetime DSM-IV or ICD-10 mood and anxiety disorders.

5. *Young Mania Rating Scale* [75]. Clinician-rated (hypo)mania symptoms were assessed monthly using the YMRS. The 11-item YMRS is the most widely studied instrument for mania, and its reliability and validity are high (Young et al., 1978).

Behavioral Tasks

1. ***MSIT-IAPS task***: The MSIT incorporates aspects of well-established measures of cognitive interference (Stroop; Simon, and Eriksen Flanker tasks), and uses two different types of cognitive interference (spatial and flanker) to measure cognitive control.[76, 77] Each trial of the MSIT is overlaid on an image from the International Affective Picture System (IAPS).[78] IAPS pictures are either neutral, positive, or negative valenced, counterbalanced between the control and interference conditions. During each trial of the MSIT, a three-digit number (comprised using the numbers 0, 1, 2, or 3) was presented for 1.7 seconds on the screen. Each set contains two identical distractor numbers and a target number that differed from the distractors. Participants report via a button press the identity of the target number that differs from the two distractor numbers (Figure 1). During Noninterference (control) trials, distractor numbers are always zeros, and the identity of the target number always corresponds to its position on the button response pad (100, 020, 003). By contrast, during Interference trials, distractor numbers are always numbers other than 0, and the identity of the target number is always incongruent with its position on the button response pad (e.g. 211, 232, 331, etc.). Trial stimuli are presented on the screen for 1.7s, followed by an inter-trial interval (ITI) fixation cross of varying lengths (Figure 1). The trial and ITI sequence is determined using Optseq2 (http://surfer.nmr.mgh.harvard.edu/optseq).[79] Trials are analyzed to examine the main effect of interference (All Interference – All Noninterference), the main effect of valence (All Negative – All Neutral; All Positive – All Neutral), and the interaction of interference and valence (Negative Interference – Negative Non-Interference; Positive Interference – Positive Non-Interference; Negative Interference – Neutral Interference; Positive Interference – Neutral Interference; Negative Non-Interference – Neutral Non-Interference; Positive Non-Interference – Neutral Non-Interference). Task behavioral performance is analyzed by calculating the average response time (reaction time, in milliseconds) and percentage of correct responses (accuracy) for each trial of interest. The MSIT-IAPS task was recently validated in BD patients (Ellard et al., in press).

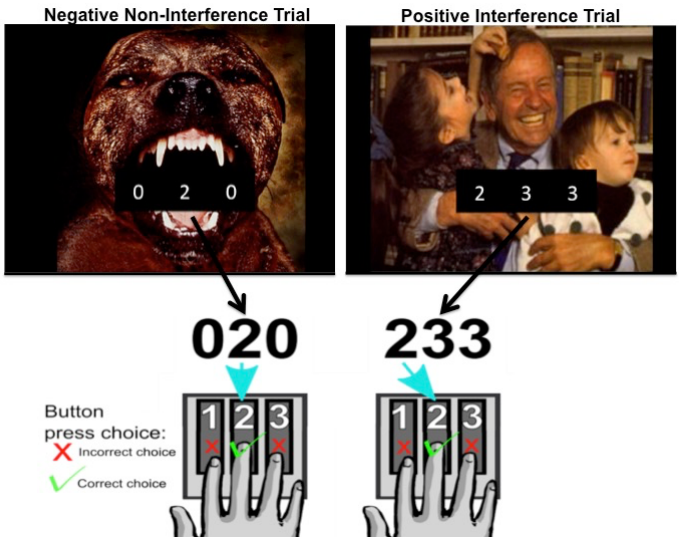


Figure 5. MSIT-IAPS task.

2. ***Emotion Conflict Resolution Task (Etkin et al., 2006):*** The ECR task is a well-validated task designed to assess the effects of emotional conflict that arises from the incompatibility between task-relevant and task-irrelevant emotional dimensions of a stimulus (Figure 6).[80] Faces with fearful and happy expressions are presented with the words "happy" or "fear" written across them. Words are either *congruent* (e.g. "happy" written across an image with a happy expression) or *incongruent* (e.g. "happy" written across an image with a fearful expression). Subjects are asked to identify the emotional expression of the face while ignoring the word. Thus, successful completion of the task requires regulation of responses to task irrelevant emotional stimuli in order to focus on task relevant goals. Trials are analyzed with regard to immediately preceding trials: incongruent trials preceded by congruent trials (CI trials) measure emotion conflict, and incongruent trials preceded by incongruent trials (II trials) measure resolution of emotion conflict. The ECR task has been validated in both healthy and psychiatric populations.

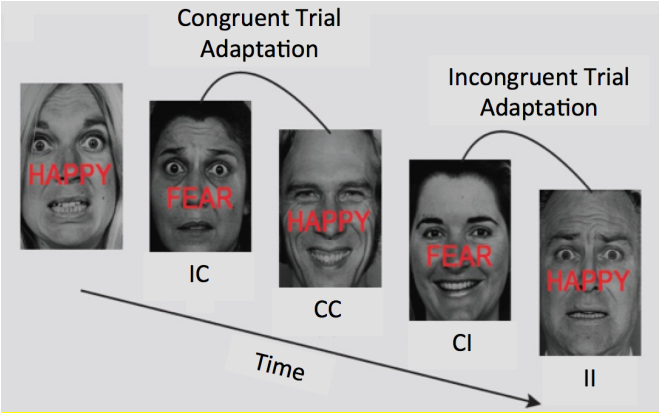


Figure 6. ECR task.

Compensation

Subjects will be compensated by check for up to $100 for completion of a protocol. The breakdown of

compensation is as follows:

• 1st Visit (Clinical evaluation, TMS, and pre- and post-TMS assessments)	$ 30
• 2nd Visit (TMS and pre- and post-TMS assessments)	$ 30
• 3rd Visit (TMS and pre- and post-TMS assessments)	$ 30
• Protocol completion bonus	$ 10
TOTAL	$ 100

Because data from all three visits (dmPFC sham, VLPFC TMS, IPL TMS) are necessary to interpret the results with causal explanatory power, participants will be paid a completion bonus for completing all three visits.

If the subject does not complete the entire study he/she will be compensated for the procedures listed above that were completed. Subjects are informed that it may take up to 4-6 weeks for them to receive their payment.

VI. BIOSTATISTICAL ANALYSIS

A. Data variables being collected for the study (Data collection sheet)

We will collect the following data variables for this study:

Demographic information:

- Age
- Gender
- Race
- Ethnicity
- Handedness
- Education level
- Parental education level
- Clinical diagnosis
- Age at onset of illness
- Medications
- Past medical history
- Smoking habits
- Substance use/abuse history
- Results from urine screening for pregnancy and drug use

Scores from clinical scales:

- HAM-D-17 (patients only)
- YMRS (patients only)
- ACS (both patients and healthy controls)
- DERS (both patients and healthy controls)

Scores from subject-completed surveys and tasks:

- MSIT-IAPS
    - Reaction time (ms)
    - Accuracy (%)
    -
- ECR Task
    - Reaction time (ms)
    - Accuracy (%)

B. Study endpoints

As this study is not a clinical trial, there is no particular outcome measure that will be indicative of a study endpoint. We will end the study when we meet our recruitment goals. In the event that we encounter any major adverse events, we will consult with the IRB to discuss whether the study needs to be terminated.

C. Statistical analysis

We will test for group differences in demographic and clinical variables using SPSS, using χ^2 and t-tests for ANCOVA as appropriate. For both MSIT-IAPS and ECR behavioral tasks, we will analyze differences in trial-by-trial reaction time slopes from pre to post stimulation between IPL, VLPFC or Sham stimulation using generalized linear mixed model regressions.

D. Power analysis (e.g. sample size, evaluable subjects)

This is a pilot study. This being the first study of its kind, it is difficult to do a formal power and sample size analysis because we do not have a measure of effect size, but given previous similar studies and our usual rate of loss to follow up, we estimate we will need 20 participants for at least 70% power to detect a medium effect size (*f*) of 0.25.

VII. RISKS AND DISCOMFORTS

Common risks of TMS procedure

Subject may feel twitching of the scalp muscles during stimulation and/or local discomfort (tapping sensation) under the coil. It is possible that the subject may feel a headache after the TMS measurement that is generally caused by keeping the head in the same position for a lengthy period of time and/or by stimulation of the scalp muscles and nerves by the TMS pulses. TMS may also induce nausea in some patients[81]. The headache or nausea, if present, is typically mild, disappears soon and can be treated by mild over-the-counter analgesics.

Although there are no reports suggesting increased risk for TMS during pregnancy, pregnant women are excluded from this study due to insufficient knowledge of the effects of the strong magnetic fields on the fetus.

Subjects are thoroughly screened by a research assistant prior to their enrollment in the study to ensure subject safety. Subjects are carefully assessed before, during, and after TMS administration by study staff to ensure that they suffer no adverse reactions.

Uncommon risks of TMS procedure

Repetitive TMS at high frequencies has the rare potential to induce a seizure even in healthy individuals (~ 8 reported cases worldwide since the invention of TMS in 1985, 1 with cTBS), but the risk for seizure can be effectively managed by using appropriate subject selection criteria and by keeping the TMS parameters within the safety parameters of the international safety consensus (Rossi et al., 2009). Compared with traditional low or high frequency TMS protocols, theta burst stimulation (TBS) uses less pulses (600 vs. 1200-1800), lower intensity (80% of AMT vs. 120% RMT) and shorter duration (40-190 seconds vs. 20-30 minutes). With such low intensity, subjects receiving TBS seldom complain of any unpleasant sensation that is seen in the other rTMS stimulation protocols, and TBS has been considered safer than other TMS protocols. Nevertheless, one should consider that theta burst stimulation uses higher frequencies, even if in a patterned manner. One single case has been reported of a seizure using TBS, but with a stimulation intensity of 100% of the RMT (higher than the currently used 80% of the AMT). Oberman and colleagues published a recent review and meta analysis of the safety of TBS, and concluded that the "general risk of adverse events during TBS is comparable to or less than other high frequency rTMS protocol (Oberman et al., 2011).

The TMS parameters used in this study will not result in long-term changes. Continuous TBS at an intensity of 80% AMT over the primary motor area produces significant inhibition of Motor Evoked Potential size lasting for 20 or 60 minutes depending on whether the stimulation is given for 20 seconds (300 pulses) or 40 seconds (600 pulses) (Huang et al., 2009).
To protect the subjects from the risk of a seizure, this study strictly adheres to the international safety consensus by using only TMS parameters that have never induced seizures in healthy subjects and by excluding subjects at increased risk for seizures (Rossi et al., 2009). In the unlikely event that a seizure occurred, the seizure would stop as soon as the TMS was stopped, and the MGH TMS clinical service safety plan would be activated, including transfer of the subject with an ambulance to MGH ER for a medical check-up. No one has ever developed epilepsy as a consequence of TMS. There are no known or foreseeable long-term risks associated with TMS.

Subjects are thoroughly screened by a research assistant prior to their enrollment in the study to ensure subject safety. Subjects are carefully assessed before, during, and after TMS administration by study staff to ensure that they suffer no adverse reactions.

Psychosocial risks

Answering questions about psychiatric history and symptoms during the psychiatric evaluation may cause anxiety or discomfort. However, participants will not be forced to answer any questions, will be given multiple opportunities to take breaks, and may completely withdraw from the study without any negative consequences. The risk of breach of confidentiality is present by extremely slight, given the precautions we take in de-identifying and protecting our data. The subject may feel mildly bored or frustrated while participating in the behavioral tasks, but he or she is free to stop at any time. Viewing images from the IAPS may also cause participants minor emotional distress, anxiety or discomfort. However, these images do not exceed graphic content found in mainstream media. Participants will be informed prior to the start of the study of this potential risk. Further, participants may terminate study procedures at any time should they experience distress.

Although we anticipate no increase in risk of suicide or self-harm as a result of study procedures or participation, we are (a) studying psychiatric patients and (b) our study procedures involve asking participants about mood symptoms. Therefore, it is possible that in the course of study participation, participants may have and/or express suicidal ideation or intent. If a research staff has any concerns about participant suicidality during a study visit, the research team will follow the plan outlined below:

1. Study staff will page study PI (Dr. Kristen Ellard), site-PI (Dr. Joan Camprodon), or covering clinician (to be designated if both Dr. Ellard or Dr. Camprodon cannot be available for a particular study visit). Study staff will discuss with the responsible PI/clinician the clinical details relating to the participant's safety/suicidality. The responsible PI/clinician will recommend a plan as is appropriate to the clinical situation.

2. If the responsible PI/clinician determines that the patient or clinical situation warrants further (i.e., a higher level of) evaluation, he/she will physically go to the location where study procedures are being conducted, evaluate the research participant in person, and act as the clinical situation warrants. If the responsible PI/clinician determines that the participant is at imminent risk of harm, the safety plan may include urgent transfer of the participant to the MGH Emergency Room via ambulance, contacting the participant's clinician, and/or other similar procedures."

   We will follow a similar plan in the event that a research participant experiences any other psychiatric symptoms that are acutely or imminently concerning (not just suicidal thoughts or thoughts of self-harm), including but not limited to confusion, agitation, severe anxiety/panic, and paranoia or other psychotic symptoms.

Informed Consent

Participants must be capable of understanding the nature of this study, its potential risks, discomforts, and benefits. Since all participants will be 18 or older, they will provide consent without parental or other guidance. The candidate will obtain informed consent after the study purpose and procedures have been fully and clearly explained, and the potential participant has demonstrated an understanding of the protocol, willingness to participate, and capacity to consent.

As a means of assessing participants' understanding of what the study entails, the candidate will conduct a one-on-one informed consent survey, which asks questions such as "What illness is being studied in this project?" "Are there any risks to participating in this study?" and "Will you lose any of your benefits if you refuse to participate in this study?" If the participant is unable to answer the questions or demonstrates a lack of understanding, the investigator will review the details of the study again. The survey therefore serves to ensure that participants are actively engaged in the informed consent process. For each participant, we will re-administer the informed consent survey at the beginning of each visit, in order to ensure that the participant is capable of consent throughout the entire study. Participants who are unable to answer questions correctly even after additional information is provided will be excluded from the study. This process is designed to enroll only participants who have the capacity to make informed decisions about participation in this research and to prevent undue influence on the subject to enroll in the study by their physician. Participants will be given a copy of the consent form, signed by them and the investigator.

Confidentiality

We will collect sensitive clinical and personal information from subjects, as well as measures related to brain function and structure. These data have personal meaning, and loss of privacy around them would result in substantial harm to all subjects, especially patients with psychotic disorders.

Thus, we will ensure that the data collected in this study remains protected and confidential. All information obtained in this study will be kept in a research office under lock and key at the MGH Martinos Center for Biomedical Imaging. Research participants will be identified by code numbers only, and no description of individual patients will be included in any publication. All databases related to the

study will be stored on a desktop computer belonging to the PI in the research office. Only the PI and her designated assistant will have access to this information. If data are shared for purposes of analysis, they will be transmitted only in pooled form and subjects will be identified by code. If data are shared, they will first be "scrubbed," or removed, of any personally identifying header information and transferred via the Partners Research Computing Secure File Transfer and Collaboration system (http://rc.partners.org/sFTP), which is secured via 256-bit SSL encryption, scans all files with anti-virus software, and is HIPAA compliant.

Subjects will be informed that all the information obtained in this study will be used for research investigational purposes only. The names of subjects will never be publicly disclosed at any time. Subjects will not be identifiable in any publication that may arise from this research. Subjects will receive a copy of the consent document to keep. Subjects will be informed that this research will be conducted and administered in compliance with all state and federal laws.

Subjects will be informed of their confidentiality rights in the informed consent form. To ensure that subjects' rights and safety are protected during the conduct of this research study, subjects consent to the inspection of medical records by specifically authorized monitors. Such monitoring may be performed by the Partners IRB, or by the FDA or other involved federal agency.

Any email communication with subjects will be done using encryption, i.e. using the "Send Secure" function in the Partners Healthcare email system. We will also discourage subjects from communicating about medical issues via non-secure email.

VIII. POTENTIAL BENEFITS

Potential benefits to participating individuals and society

Subjects are informed that there is no direct benefit to them from participating in this study. As mentioned in the section on Background and Significance, the potential benefits to society are increased understanding emotion regulation in bipolar mood disorders and the role prefrontal cortex regions (VLPFC, IPL) play in adaptive regulation. The current research, which uses TMS as a tool to investigate with causal explanatory power the role of the VLPFC and IPL in emotion regulation in bipolar disorders may provide the basis for the development of TMS as a potential treatment tool in such disorders in the future.

IX. MONITORING AND QUALITY ASSURANCE

Human Subjects Protections:

See Section VI (Risks and Discomforts) for measures to protect research subjects from the risks associated with the informed consent process, confidentiality, psychiatric evaluations, and TMS procedures.

Independent monitoring of source data

Kristen Ellard, PhD., the Principal Investigator (PI), will be responsible for monitoring the validity and integrity of the data, as well as adherence to the protocol. She will be present for the informed consent procedures, assessments, and TMS administration for the first several subjects and closely supervise the training of all study staff involved in carrying out this research. In addition, co-investigator Joan Camprodon, MD, will be on-site at the MGH Laboratory for Neuropsychiatry and Neuromodulation in

the Charlestown Navy Yard Campus, to monitor the correct and safe administration of TMS for each subject.

Standard operating procedures (SOP) will be written, routinely followed, and updated as necessary to ensure adherence to the IRB-approved protocol. Any time there is a change in study staff, the PI will again provide direct hands-on training in order to ensure that all procedures are conducted in adherence with the IRB-approved protocol and that the data collected are of high quality, validity, and integrity. Moreover, the PI will meet at least once a week with the study staff to review any issues and data quality. Finally, the PI will be responsible for subsequently signing all consent forms, thereby allowing her to monitor the informed consent process on a consistent basis. The research coordinator and PI will report any minor deviations from the protocol at each yearly continuing review. Major deviations will be reported within 5 working days of the incident's occurrence or detection.

Safety monitoring (e.g. Data Safety Monitoring Board, etc.)

The current research uses standard nonsignificant risk applications of TMS in the context of a physiological/cognitive study, not a therapeutic clinical trial; thus reporting of adverse events to the FDA is not applicable. Given the relatively low risk posed by the study we do not feel that monitoring by a DSMB is necessary.

Outcomes monitoring

All subjects' clinical data will be coded with research numbers that do not contain any identifying information. The code linking the research number to personal identifying information will be stored in a password-protected encrypted computer file on a locked computer in a locked office at the Martinos Center. Subject interview information is stored in locked file cabinets in locked rooms at the Martinos Center.

Medical Follow-up and Referrals

Participants who test positive on the urine pregnancy test conducted as a part of this research study will be informed of the positive test result and recommended to follow-up with their primary care doctor or other physician. Participants who wish to speak with a medical doctor about the test results will be offered the opportunity to consult with the study PI.

Reporting of Adverse Events

As soon as the PI or a member of research staff learns of an adverse event, he/she will first consider the immediate safety of the patient. If the patient is not safe, either to him/herself or others, the member of the research staff/PI will take appropriate steps to acutely stabilize the patient. Members of the research staff will defer to the PI's judgment. If there is an adverse event without an imminent safety concern, then the person who learned of the adverse event will call the PI and/or other members of the research staff and decide the best course of action to deal with the event, guided by the principles of Human Subjects research. They will then submit an adverse event report to the IRB and regulatory officials using the Research Subject Report of Adverse Event form, according to the PHRC reporting guidelines, within 5 working days or 7 calendar days of the date they become aware of the problem.

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