Official Title: Establishing the effect of electroencephalography (EEG)-guided theta burst stimulation on reducing mania/hypomania-related affect and reward driven behavior in Bipolar Disorder

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Project title: ***Establishing the effect of electroencephalography (EEG)-guided theta burst stimulation on reducing mania/hypomania-related affect and reward driven behavior in Bipolar Disorder***

***Intended area of focus*: Bipolar Disorder: proof of concept studies for novel treatment approaches, and the advancement of the application of neural devices to bipolar disorder**

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Technical abstract

Current Bipolar Disorder (BD) treatments are often ineffective because of lack of efficacy and/or severe side effects, especially related to the commonly prescribed medications for the defining BD symptom, mania/hypomania. There is therefore a critical need to develop new, more targeted treatments with fewer side effects to treat and reduce recurrence of mania/hypomania in sufferers of BD, which are guided by an in depth understanding of the neurobiological mechanisms predisposing to this defining symptom of BD.

Specific behavioral traits, including elevated reward sensitivity, sensation seeking and impulsivity, predispose to mania/hypomania and mania/hypomania-related reward-driven impulsive behavior, e.g., steep delay discounting, the often disadvantageous preference for immediate, smaller vs. delayed, larger rewards. These behavioral traits, and thus mania/hypomania and reward-driven impulsive behavior, can be triggered in reward expectancy contexts, i.e, waiting for a reward, in people with BD. During these contexts, including when choosing an immediate-smaller vs. a delayed-larger reward, we showed abnormally elevated reward neural network (RNet) activity, especially in left ventrolateral prefrontal cortex (vlPFC), in adults with BD. Electroencephalography (EEG) provides more affordable, available and translational measures of neural activity than other brain imaging methods such as fMRI. We reported that beta frequency EEG activity (beta power) during reward expectancy is elevated in adults prone to BD. These findings add to the literature highlighting the left vlPFC in reward evaluation, and indicate that this region is abnormally active during reward expectancy in people with BD. By contrast, higher beta power in the central executive network (CEN), including right dorsolateral prefrontal cortex (dlPFC), guides the often more advantageous choice of delayed, larger rewards, i.e., less steep delay discounting.

Theta burst stimulation (TBS) is a non-invasive neuromodulation technique that can target the RNet left vlPFC, and/or the CEN, and has great promise as a novel intervention to delay or prevent onset/recurrence of mania/hypomania and reward-driven impulsive behavior, a critical step to prevent mood cycling in BD. *Our goal is to determine if TBS modulation of RNet and CEN reduces mania/hypomania-related affect (mania risk) and reward-driven impulsive behavior, as a first step to developing new treatments for BD.*

We aim: **1.** *To examine acute TBS-induced changes in RNet and CEN EEG beta power during a delay discounting task in BD (manic/hypomanic, euthymic) adults (18-35 yrs, to avoid confounds of long illness history)*. When choosing between reward options, we hypothesize that BD adults will show reduced EEG beta power and functional connectivity (FC) in left vlPFC and wider RNet during the choice phase of the task after inhibitory (continuous) TBS (cTBS) over left vlPFC; and elevated EEG beta power and FC in right dlPFC and wider CEN during the choice phase of the task after excitatory (intermittent) TBS (iTBS) over right dlPFC (each vs. control TBS: cTBS over left somatosensory cortex, Som). **2.** *To determine how TBS-induced changes in RNet/ CEN beta power impact mania/hypomania-related affect and delay discounting.* We hypothesize that greater reductions in left vlPFC-RNet beta power and FC after cTBS over left vlPFC, and greater increases in right dlPFC-CEN beta power and FC after iTBS over right dlPFC, will lead to greater reduction in mania/hypomania-related affect and delay discounting than after cTBS over left Som.

In exploratory analyses, we will: **1.** compare effects of left vlPFC cTBS vs. right dlPFC iTBS on affect and impulsive behavior; and **2.** determine if the above behavioral traits moderate TBS-induced effects.

Significance. The importance of understanding the neural basis of predisposition to mania/hypomania. Bipolar Disorder (BD) is debilitating and common, and defined by a history of mania/hypomania[1]. Yet, current treatments are often ineffective because of their lack of efficacy and/or severe side effects, especially related to the commonly prescribed medications for mania/hypomania[2]. *There is therefore a critical need to develop new, more targeted treatments with fewer side effects to treat and reduce recurrence of mania/hypomania, guided by an in depth understanding of the neurobiological mechanisms predisposing to this key BD symptom.* Elucidating causal relationships among neural and behavioral measures underlying predisposition to mania/hypomania *can provide neural targets for new interventions to prevent mania/hypomania in individuals at risk for BD, prevent mania/hypomania recurrence in euthymic BD individuals, and treat other disorders associated with reward-driven impulsive behavior.*

Which behaviors predispose to mania/hypomania? Certain behavioral traits, including reward sensitivity, drive, sensation seeking (RS-Drive-SS) and impulsivity, characterize BD, predispose to mania/hypomania and reward-driven impulsive behaviors, and can be triggered in reward expectancy contexts[3,4]. One such context, intertemporal decision making, involves choosing between an immediate, smaller vs. a delayed, larger reward. Due to high levels of the above traits, individuals with BD tend to have higher expectation of (more immediate) future rewards[5,6], and as a result often show a disadvantageous preference for immediate, smaller vs. delayed, larger rewards, known as steep delay discounting[7].

Increasing evidence indicates that neural activity in the left ventrolateral prefrontal cortex (vlPFC) is elevated in BD adults during reward expectancy[8], and that the left vlPFC and other reward network (RNet) regions (e.g., orbitofrontal cortex, anterior cingulate cortex, striatum and midbrain) support reward-driven impulsive behavior during intertemporal decision making[9,10]. Compared with functional Magnetic Resonance Imaging (fMRI), EEG is more readily available and affordable, even outside major academic centers. Furthermore, greater reward-related frontocentral cortical beta (β) band EEG power is associated with high pleasure and sensation seeking (SS)[11]. By contrast, the central executive control network (CEN), comprising dorsolateral prefrontal cortex (dlPFC), inferior parietal cortex and dorsal anterior cingulate cortex[12], promotes longer-term, larger reward choice, i.e., less steep delay discounting[10.] Yet, no studies examined the neural basis of intertemporal decision making in BD adults.

Neuromodulation approaches. Transcranial magnetic stimulation (TMS) and theta burst stimulation (TBS) are non-invasive neuromodulation techniques applied to healthy and psychiatric populations[13]. TBS is a TMS paradigm that consists of a 3-pulse, 50 Hz burst every 200ms (theta frequency range), and can increase when applied intermittently (iTBS), and decrease when delivered continuously (cTBS), the excitability of cortical neurons[14]. *By modulating activity in the RNet and CEN, TBS can establish causal brain-behavioral relationships, as a first stage to developing novel, more targeted treatments for BD.*

Summary. ***Aim 1*** will examine acute, TBS-induced changes in left vlPFC and wider RNet β EEG power and FC, and right dlPFC and wider CEN β power and FC, during a delay discounting task in BD adults; and ***Aim 2*** , the impact of these TBS interventions on mania/hypomania-related affect and delay discounting. We will explore whether baseline RS-Drive-SS and impulsivity behavioral traits moderate TBS-induced acute changes in EEG parameters, mania/hypomania–related affect, and delay discounting. To achieve these aims, we will compare the effects of cTBS to the left vlPFC and iTBS to the right dlPFC (each versus control condition TBS, cTBS to the left somatosensory cortex, Som) in 20 manic/hypomanic or euthymic adults with BD (for a range of mania/hypomania-related affect severity; type I/II; 3-fifths manic/hypomanic).

Innovation. This will be the first study to use an interleaved EEG/TBS/EEG design during delay discounting to elucidate the causal roles of left vlPFC and right dlPFC in predisposition to mania/hypomania and reward-driven impulsive behavior, to provide neural targets to help develop novel BD treatments.

Feasibility data. Acute TBS-induced changes in β power. We collected preliminary EEG data during a delay discounting task before and after TBS in 3 BD (31.6±8 yrs; 1 female; 2 euthymic, 1 depressed, type I) and 2 healthy (32.3±9 yrs; 1 female) adults. Pre-TBS, left vlPFC β power prior to choosing immediate, smaller

rewards was higher in BD (0.32±0.40 μv^2) vs. healthy (-0.20±0.55 μv^2) adults. Left vlPFC β power post versus pre TBS prior to choosing immediate, smaller rewards was reduced after left vlPFC but not after left Som cTBS in BD adults (**Fig. 1**; EEG cortical source maps (right) are in the 3 BD adults before (top) and after (bottom) left vlPFC cTBS; color bars: current source density distribution normalization). We showed a positive relationship between SS and left vlPFC β EEG power in healthy adults during uncertain reward expectancy on a card guessing task [15], thus providing feasibility of examining RS-Drive-SS, impulsivity-TBS-induced EEG change relationships.

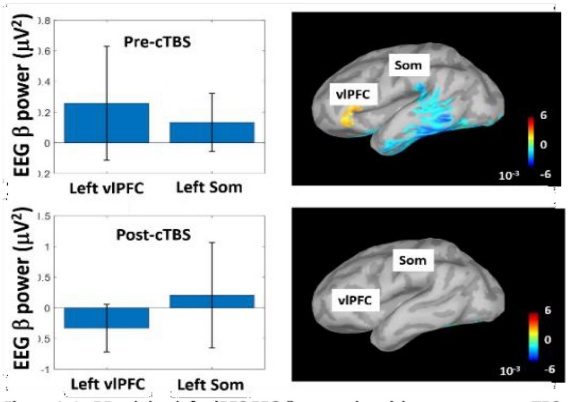
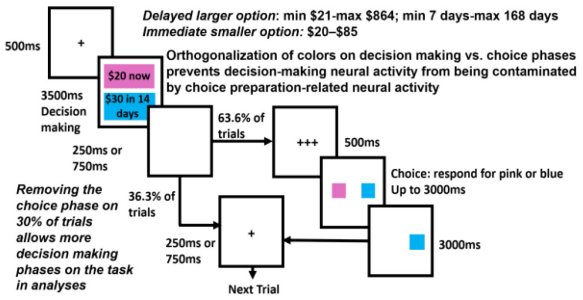


Figure 1: In BD adults, left vlPFC EEG β power (y axis) post versus pre TBS during intertemporal decision making prior to choice of immediate, smaller rewards was decreased after left vlPFC but not left Som cTBS (x axis)

<u>Research Design and Methods.</u> Participants. We will perform assessments on 25 manic/hypomanic or euthymic adults with BD (3-fifths manic/hypomanic;18-35 years, to avoid potential confounds of long illness history on EEG measures; 50% female; racial subgroups reflecting the distribution of different racial populations in Pittsburgh), to have useable data in n=20 across all assessments. BD will be defined using SCID-5 criteria[16]; standardized mania[17], depression[18,] and anxiety[19] rating scales will measure respective symptom severity. *Psychotropic medications*: any combination (except antidepressant monotherapy) of atypical antipsychotics, lithium, other mood stabilizers, and antidepressants taken for >2 months, as these are commonly prescribed medications for BD. *Exclusion criteria:* Personal and family history of epilepsy, binge alcohol drinking, SNRI antidepressants, bupropion and stimulants, as they can elevate seizure risk, a contraindication for TBS. Additional inclusion and exclusion criteria are as previously reported[20]. We will screen 63 adults with BD recruited from local clinics, to scan 25 (60% screen failure), to obtain usable sMRI and fMRI and useable *<u>three</u>* EEG/TBS session data in <u>≥</u>20 BD adults, assuming 20% fMRI and EEG data loss and attrition. Recruitment will be over 10.5 months to allow project set-up (3 weeks), and analyses at the study end (3 weeks). *Total RS, Drive, SS[21] and total impulsivity[22] will be assessed and used in exploratory moderation analyses* (below). All the above and study consent will be administered at the screening visit.

Baseline scan. This will be ~1 week before the 3 EEG/TBS/EEG sessions. Each participant will undergo structural MRI (sMRI); and fMRI during the delay discounting task (**Fig. 2**). Task-evoked activation with fMRI will constrain the spatial locations of EEG sources in neural regions of interest[23.]

Figure 2: Delay discounting task
Two (hypothetical) options: smaller immediate (pink) and larger delayed (blue) reward



<u>fMRI version (above):</u> 17 min (2, 8.5 min blocks) event-related task.132 trials . Amount and delay ranges are modeled on the Kirby delay discounting task (1). Participants also perform a risk preference questionnaire (2) post scan based on the Kirby scale (replacing delays with probabilities) to correct for subjective value non-linearity, which can bias delay discounting parameters
<u>EEG version:</u> 30 min (4, 7.5 min blocks); 260 trials (65/block); choice phase=2s, delay duration and amounts presented only in the last 1s to reduce variability in reading

TBS neurotargeting, dosing. Baseline sMRI (MPRAGE) images will be imported into a TMS neuronavigational system (Localite, Ltd) for stereotaxic registration with the TMS coil, and identification in 3D of left primary motor cortex (for individual resting motor threshold, RMT), left vlPFC, and a control cortical region, left somatosensory cortex (Som), using anatomical landmarks. The software will mark the location and trajectory of the TMS coil, improving anatomical accuracy across participants. TBS dosing (110% of RMT) is based on studies targeting orbitofrontal and ventromedial prefrontal cortices[24]. Meta-analyses of cTBS over motor cortex suggest reliable decreases in motor evoked potentials for 50-60min after 40s cTBS[25], longer than the post-TBS time interval when we will start and run EEG acquisitions during the delay discounting task. Effects of similar TBS protocols extend to dlPFC and medial prefrontal cortex[26]. Safety and tolerability of iTBS and cTBS to prefrontal

cortex was established in our completed study (R21MH112770). After determining RMT, Simulation of Non-Invasive Brain Stimulation (SimNIBS) will identify the cortical target (at baseline scan) for TBS, to ensure that the electric field generated by TBS at 110% RMT is focused on left vlPFC/right dlPFC/ left Som. **EEG/TBS/EEG sessions** include left vlPFC cTBS, right dlPFC iTBS, and left Som cTBS; max. 3 hours each. These will occur over approx. 2-3 weeks. A random number sequence will be generated by co-I Dr. Coffman for the EEG/TBS/EEG session order to which each participant is assigned. All personnel other than the research associate administering TBS will be blind to TBS condition. *TBS order will be counterbalanced across participants.* Debriefing that payments are fixed will be after the final session.

Affect will be measured by the PANAS[27] (acute positive, negative affect) before and immediately after each TBS session. We will also administer the PANAS, and ask if suicidal ideation and aggressive urges are present, at 1 and 2 hrs after each TBS session*. If a participant experiences large and/or sustained increases in negative/positive affect, and/or new/potentially harmful symptoms (e.g., suicidal/homicidal ideation), s/he will be immediately referred to psychiatric services.* Study staff will assess participants prior to EEG and TBS on each TBS day, to ensure that they meet inclusion criteria. *If these assessments suggest a severe manic/hypomanic or depressive episode, participants will be excluded and referred to psychiatric services.* **EEG** during the delay discounting task (**Fig. 2**; references in figure: (1)[28];(2)[29]) will be collected immediately before and after TBS. **TBS** will be performed using the MagPro X100 (MagVenture, DK): ***cTBS:*** 1200 pulses in a theta burst pattern (bursts of 3 pulses at 50 Hz repeated at 5 Hz): 2 x 40s blocks of 600 pulses (200 x 3 pulse bursts) each: 1st block with an intensity ramp-up to improve tolerability, and the 2nd block at full intensity 110% RMT, over left vlPFC or left Som. ***iTBS:*** two blocks of 20, 2s trains (30 pulses), 8s intertrain intervals, for a total of 192s per block. **Discomfort.** Participants will rate itchiness, tingling, heat, pain on a 10-point scale (1=none; 10=most severe) at the start and end of TBS. We will examine subsequent effects of TBS on affect. Participants can withdraw from the study if they are unable to tolerate the procedures.

EEG data source localization and preprocessing. Using Brainstorm, sensor locations will be registered to Human Connectome Project-/SimNIBS-generated tissue surfaces/volumes. Task-evoked fMRI activity will constrain the spatial locations of EEG sources in RNet and CEN cortical regions. Analyses of β (15-30 Hz) power in and phase synchronization among these regions will be calculated from source-resolved EEG frequency decomposition using complex wavelets. FC will be quantified using phase locking and phase coherence[30]. Parametric regression will predict β power and FC to the primary condition on the delay discounting task (below). <u>*Atlas-defined ROIs*</u>: right and left regions in native space using FreeSurfer.

A priori EEG measures. We focus on changes (pre TBS to post TBS) in β power in left vlPFC (and right vlPFC, in case of weaker lateralization in some participants), and β FC between these regions, and with other RNet regions; and β power in right (and left) dlPFC, and β FC with other CEN regions, to the primary task condition (below). **Secondary EEG measures:** β power and FC in/ among other RNet and CEN regions.

EEG data primary stimulus condition: intertemporal decision making before choosing immediate, smaller reward options, and before choosing delayed, larger reward options. **Primary reward-driven impulsive behavior measure:** k value (discounting of delayed larger rewards), which is obtained via model fitting using the Variational Bayesian Analysis toolbox, using an exponential or hyperbolic discounting function. **Secondary behavioral measure:** number of immediate choices.

Analytic approach. Transformations will render distributions more Gaussian as needed. Data reduction methods (e.g., principal components, factor analysis) will reduce the number of a priori vlPFC-focused and dlPFC-focused EEG measures to a conservative number of components/ factors vs. number of participants (~1 measure: 10 participants) in analytic models. There will be: 2 affect (2 PANAS, above); and one behavior (k) measure in each model. <u>*Covariates:*</u> age, BD onset age, gender, SES, yrs. of education, menstrual cycle phase (self-report). Family psychiatric illness history, history/current alcohol/nicotine/cannabis use per week, psychotropic medication (yes/ no to each class), psychotherapy, previous COVID-19 (yes/no). Penalized regression (e.g., elasticnet) will reduce the number of covariates

to those with strongest relationships with dependent variables (DVs), to have ~1 covariate: 10 participants in each model. No studies examined effects of TBS on EEG measures in BD. We assume a medium effect size, as shown previously for TBS vs. control conditions[31]. For power calculations for the main analysis of the single *overarching* model in each hypothesis, we use alpha=0.05 and report the smallest effect size with power .80. For subsequent tests, e.g., testing M moderators, we use a Bonferroni corrected alpha.

Hypothesis testing and power. H1.1, 1.2 (Acute cTBS over left vlPFC vs. iTBS over right dlPFC and cTBS over left Som on EEG, affect and behavior measures). We will use a within-group repeated measures ANCOVA, with n=20 and 3 repeated TBS conditions: DVs=max. 3 EEG measures and 2 affect (PANAS) +1 behavior (k-value) measures. Conservatively assuming a within-subject correlation of 0.5, we have power .80 to detect a medium effect size, f^2=0.32, of TBS condition. **H2** (Relationships among RNet and CEN EEG and affect (2 measures) and delay discounting (k parameter) changes). Multiple regression will examine relationships among changes in EEG and affect and k values in and among the different TBS conditions. A correlation matrix for the 3 EEG and 3 affective/behavioral change measures will first be computed. We hypothesize that the 9 correlations between the two types of measures will be positive. Next, a multivariate regression model will be used, with EEG measures as independent variables (IVs), and affect and behavioral measures as DVs. In all n=20 measured thrice, assuming a within-subject correlation of r=0.5, we can detect a medium effect size of f^2=0.24. **Exploratory analyses** (Moderating effect of behavioral traits). With 2 moderators (2 behavioral traits; above), we have .80 power to detect a medium moderator effect size d=0.45, using alpha=0.05/2=0.025[32]. **Secondary analyses** will use similar models, with secondary EEG measures. **Rigor, Reproducibility.** 1) Diagnostic and behavioral measures have good psychometric properties. 2) MRI data undergo regular quality controls; EEG-TBS will be performed using established procedures and safety guidelines. 3) Participants and staff will be blinded to TBS condition. **Future work** will examine effects of repeated TBS on mood and reward-driven impulsive behavior in euthymic and manic/hypomanic BD adults. **Limitations:** As there are two active TBS conditions, an active control TBS condition was necessary. Left Som cTBS is a suitable control TBS condition in our pilot data, and see[33]. No sham condition was possible due to participant burden and time constraints. It was not possible to recruit more BD adults in 1 year; we have sufficient power for main effects. Recruiting healthy controls was also beyond the 1-year time frame and budget; instead, we include a TBS control condition.

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