Accelerated Theta Burst Stimulation for Inpatients with Bipolar Disorder

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Study Protocol Title: Accelerated theta burst stimulation for inpatients with bipolar disorder.

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Academic Sponsor: David Spiegel
Study site: Stanford University

Research Synopsis

This open-label pilot study aims to establish the safety of an accelerated intermittent theta burst stimulation (aiTBS) transcranial magnetic stimulation (TMS) protocol in patients experiencing mania or hypomania. aiTBS is an accelerated repetitive transcranial magnetic stimulation (rTMS) protocol in which 10 sessions of intermittent theta burst stimulation (iTBS) rTMS are given each day over five consecutive days. 30 participants will receive aiTBS over the right dorsolateral prefrontal cortex (DLPFC) with the Magventure MagPro X100 rTMS system. Their responses to the treatment will be measured with assessments measuring manic symptoms (Young Mania Rating Scale [YMRS], Altman Self-rating Mania Scale [ASRM], psychosis (Brief Psychiatric Rating Scale [BPRS]),, depression (Montgomery-Asberg Depression Rating Scale [MADRS]), and overall mental illness (Clinical Global Impression scale-Severity [CGI-S] and CGI-improvement [CGI-I]). Electroencephalography (EEG) will also be employed to measure resting EEG response to aiTBS and effective cortical connectivity via TMS-evoked potential (TEP) response. Heart rate variability (HRV) is another potential biomarker of mania/hypomania and has been used as a measure of TMS responsiveness in depression (Iseger *et al.*, 2017, 2021). HRV monitoring will be employed here to investigate this variable in mania as well. Participants will be treated until they become euthymic, as measured by YMRS <7 or up to 5 days, whichever comes first. Our hypothesis is that this treatment will be well-tolerated by participants and few to no serious adverse events (SAEs) will occur.

Background and Significance

Approximately 4.8% of adults will have a bipolar episode each year (Merikangas *et al.*, 2011; Miller, Dell'Osso and Ketter, 2014), and standard of care pharmacotherapies have relatively high rates of treatment resistance (Gitlin, 2006). This study is motivated by recent findings in the neuromodulation field suggesting that high-frequency (HF) rTMS (20 Hz) over the right DLPFC can treat symptoms of acute mania/hypomania in bipolar disorder (Grisaru *et al.*, 1998; Saba *et al.*, 2004; Praharaj, Ram and Arora, 2009; Tee and Au, 2020). An early double-blind controlled trial demonstrated the right DLPFC was superior to the left in treating mania in 16 patients (Grisaru *et al.*, 1998). A second open-label study in 8 patients confirmed that HF-rTMS over the right DLPFC reduced symptoms of mania (Saba *et al.*, 2004). A 41 patient single-blind randomized sham-controlled study further supported this work demonstrating that HF-rTMS over the right DLPFC was a well-tolerated and decreased measures of mania compared to the sham group (Praharaj, Ram and Arora, 2009). In these trials, patients were treated with standard of care pharmacotherapy plus rTMS as with this trial.

Other recent findings in neuromodulation have demonstrated the effectiveness of accelerated rTMS, TBS, and accelerated TBS protocols in mental illness. For example, sham-controlled trials of accelerated protocols in depression have demonstrated safety, tolerability, and efficacy (Baeken *et al.*, 2013, 2014, 2015). Further, iTBS has demonstrated equivalent efficacy to FDA-approved HF-rTMS protocols in depression (Li *et al.*, 2014; Blumberger *et al.*, 2018). Lastly, accelerated iTBS (aiTBS) such as aiTBS has not only proven safe and tolerable, but has also demonstrated higher response and remission rates for treating depression (Williams *et al.*, 2018; Cole *et al.*, 2020). These developments motivate the use of this novel and efficacious protocol, aiTBS, in treating other mental illnesses.

This is the first clinical trial investigating the application of aiTBS in bipolar disorder. The rationale for the use of aiTBS over the right DLPFC to treat mania is based on the safety, tolerability, and effectiveness of HF-rTMS over the right DLPFC in mania/hypomania (Grisaru *et al.*, 1998; Saba *et al.*, 2004; Praharaj, Ram and Arora, 2009), and the safety, tolerability, and efficacy of aiTBS in treating depression (Williams *et al.*, 2018; Cole *et al.*, 2020). Additionally, two cases applying conventional daily iTBS for the treatment of mania demonstrated efficacy (Muir *et al.*, 2018). We expect this study to demonstrate safety, tolerability, and efficacy in treating mania and to motivate larger sham-controlled trials in the future.

Public Health Impact: Completion of the proposal will provide evidence supporting a safe, tolerable, and effective treatment in a high-risk group of psychiatric inpatients. RTMS will be administered on the inpatient psychiatry unit during acute illness: a time point that is both practical and generalizable. This treatment has the potential to shorten manic episodes and hospital stay, but may also provide enduring effects that prevent future episodes of bipolarity. That is, a rapid-acting anti-mania treatment would reduce overall healthcare costs by decreasing length of stay and readmission rates.

Preliminary data: We recently completed our outpatient RCT using aiTBS in which we randomized 32 participants with highly treatment resistant depression (TRD; Maudsley Staging Method score ≥7) and treated 29 subjects. Two subjects withdrew before starting and one subject was excluded after being determined to not meet inclusion/exclusion criteria. We observed an extremely high rate of overall remission of depression where 86% of individuals experienced remission at some point during the 4 week followup period in the active group (12/14, MADRS≤10) versus a very low rate of remission in the sham group (13%; 2/15). We found an average reduction of 66% in depression symptoms (MADRS) immediately after aiTBS in the active group vs. 6% in the sham group. 10/14 participants showed ≥50% reduction in symptoms in active versus 2/15 in sham and 8/14 (57%) remitting from depression after 5 days of aiTBS in active versus 0/15 in sham, despite having failed numerous medications and psychotherapy. We followed these individuals for 4 weeks and there was a median 65-82% reduction in the MADRS during this period. At one month post-aiTBS, 64% of active-group participants continued to be responders and 43% were still in full remission, despite being 1 month after the last treatment. Mean MADRS remained significantly lower than baseline at the one-month follow up. These results provide substantial evidence that aiTBS is a safe, rapid-acting, and enduring treatment for mental illness. The outcomes of aiTBS for depression motivate us to explore the safety, tolerability, and efficacy of aiTBS in other applications such as mania.

The Effects of rTMS on right DLPFC in mania: RTMS over the right DLPFC has demonstrated safety, tolerability and efficacy in treating the symptoms of mania (Grisaru *et al.*, 1998; Saba *et al.*, 2004; Praharaj, Ram and Arora, 2009; Pathak, Sinha and Praharaj, 2015). Further, two published cases have demonstrated efficacy of iTBS protocols in treating mania (Muir *et al.*, 2018). These trials applied a conventional daily rTMS treatment schedule. Our aiTBS protocol is unique in that it applies a higher-dosage of rTMS with consideration of a modern understanding of spaced learning (Smolen, Zhang and Byrne, 2016; Etkin *et al.*,

2019) and advanced targeting (Williams *et al.*, 2018). This accelerated form of iTBS allows for the possibility to treat acute mania in the inpatient hospital setting.

Important to the present study:

Objectives

Primary objective

1. To assess the safety and feasibility of active aiTBS in hospitalized patients with bipolar disorder I and II as defined by adverse events and study retention rates (measured as actual recruitment/recruitment milestones).

Secondary objective:

1. To determine the preliminary anti-manic efficacy of active aiTBS in hospitalized patients with bipolar disorder I and II as measured by a significant reduction in the Young Mania Rating Scale (YMRS) from baseline to the immediate post-treatment visit.

Exploratory objectives:

1. To determine the preliminary anti-manic efficacy of active aiTBS in hospitalized patients with bipolar disorder I and II as measured by a significant reduction in the Altman Self-rating Mania Scale (ASRM) from baseline to the immediate-post treatment visit.
2. To determine if higher cortical response to TMS (as measured by resting EEG and TMS-EEG at baseline and immediate-post visit) is correlated with the anti-manic effects of aiTBS as measured by baseline, daily, and immediate post YMRS assessments.
3. To determine if an increase in HRV (as measured with a Neuroconn device) from baseline to the immediate-post visit is correlated with the anti-manic response to aiTBS as measured by baseline, daily, and immediate post YMRS assessments..
4. To determine the functional connectivity changes in the brain as measured by resting-state functional MRI from baseline to immediate-post treatment visit following an aiTBS intervention over the right DLPFC in inpatients with bipolar disorder I and II experiencing symptoms of mania.

Study Design/Methodology

Phase: This is a Phase II clinical trial.

Trial Design: open-label

Methods to minimize bias: This study will minimize bias via its inclusion and exclusion criteria and the use of validated laboratory and interview/self-report measures. Explicit hypotheses and corresponding planned statistical analyses, power estimates, careful consideration of potential confounds. All experimental details will be reported in a fully transparent manner to support replication.

Dose Escalation: TMS stimulation dose will be individually determined according to 90% rMT plus depth correction, and then the aiTBS protocol will be administered with a consistent dose across all participants receiving active stimulation of 18,000 pulses/day and 90,000 pulses/course.

Study Arms: One arm, active open-label

Site(s): Single Site (Department of Psychiatry & Behavioral Sciences, Stanford University)

Name of Study Intervention: Accelerated theta burst stimulation for inpatients with bipolar disorder

Interim Analysis: N/A

Stratification: None planned.

Study Population

We will enroll 30 participants in this open-label active Phase II Trial. The target population is adults of all genders and ethnicities who are between 18 and 80 years of age with bipolar affective disorder I or II and who are otherwise in good general health. Participants must be without contraindications to Magnetic Resonance Imaging (MRI) or transcranial magnetic stimulation (TMS) and must be able to attend all study visits.

Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Male or female, between the ages of 18 and 80 years at the time of screening.
2. Able to read, understand, and provide written, dated informed consent prior to screening. Proficiency in English sufficient to complete questions and follow instructions during fMRI assessments and aiTBS interventions
3. Stated willingness to adhere to all study procedures, including availability for the duration of the study, and to communicate with study personnel about adverse events and other clinically important information
4. **Primary diagnosis of Bipolar I or II Disorder** according to the Diagnosis and Statistical Manual of Mental Disorders, 5th edition (DSM-5)
5. Currently experiencing a **hypomanic or manic episode** according to the criteria defined in the Diagnosis and Statistical Manual of Mental Disorders, 5th edition (DSM-5)
6. **YMRS score of ≥12** at screening.
7. Access to ongoing psychiatric care after completion of the study.
8. Must be adherent or agreeable to pharmacotherapy per clinical standard of care at screening.
9. Patients who are in both voluntary and involuntary hold.
10. In good general health, as evidenced by medical history.
11. For females of reproductive potential: use of highly effective contraception.

Exclusion Criteria

1. Currently **pregnant or breastfeeding**.

2. Primary psychiatric condition **other than Bipolar I or II Disorder requiring treatment** other than stable comorbid anxiety disorder.
3. Diagnosis of Intellectual Disability or Autism Spectrum Disorder
4. Current **moderate or severe substance use disorder** or demonstrating signs of **acute substance intoxication or withdrawal**
5. **Active suicidal ideation** (defined as an M-SSI > 8)
6. History of **significant neurologic disease**, including dementia, Parkinson's or Huntington's disease, brain tumor, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma
7. Contraindication to receiving rTMS (e.g., metal in head, history of seizure, known brain lesion)
8. Contraindication to MRI (e.g. ferromagnetic metal in their body)
9. Treatment with another investigational drug or other intervention within the study period
10. Any other condition deemed by the PI to interfere with the study or increase risk to the participant
11. Current unmanageable psychosis that the PI believes would interfere with treatment
12. Any history of psychosurgery
13. Depth-adjusted aiTBS treatment dose > 65% maximum stimulator output (MSO).
14. Any other condition deemed by the PI to interfere with the study or increase risk to the participant.

The effects of rTMS on the developing human fetus are largely unknown (Eryılmaz *et al.*, 2015). Accordingly, we will not be enrolling pregnant women to this study. Women of childbearing potential must agree to use adequate contraception (hormonal / barrier method of birth control or abstinence) prior to study entry and for the duration of study participation. Females of childbearing-age will have a pregnancy test prior to starting the rTMS stimulation course. Should a woman become pregnant or suspects she is pregnant while participating in this study, she should inform study staff.

Participants taking certain psychoactive medications will be assessed for safety by the PI, due to potential for increase of seizure risk (Pisani *et al.*, 2002) and change in cortical excitability (Minzenberg and Leuchter, 2019).

Individuals older than 80 years of age will be excluded for the following reasons:

1. Even though the study depth adjusts individuals with greater prefrontal over primary motor cortex atrophy, the safety limit is at 120% and some individuals require greater than 120% depth adjustment to reach PFC (Kozel *et al.*, 2000; Sabesan *et al.*, 2015). With this, there is evidence of reduced efficacy in those individuals with advanced age (Freitas *et al.*, 2011; Abellaneda-Pérez *et al.*, 2019).
2. There is evidence of reduced plasticity in individuals with advanced age with a reduction in the duration of the effects of TBS (Freitas *et al.*, 2011; Abellaneda-Pérez *et al.*, 2019) which may impact the response to the approach.

Study Interventions:

Active aiTBS Intervention: We have previously discussed this stimulation approach with the FDA and the FDA deemed the approach nonsignificant risk (NSR). aiTBS will be delivered similarly to previous aiTBS studies (Williams *et al.*, 2018; Cole *et al.*, 2020) using the MagVenture MagPro X100 (Skovlunde, Denmark) TMS device equipped with a Cool-B65 A/P coil or Cool D-B80 A/P coil. The right DLPFC target will be

localized for each participant via Montreal Neurological Institute (MNI) coordinates applied to a T1 structural MRI using a Localite TMS Navigator (Siddiqi *et al.,* 2020). The right dorsomedial (DM) PFC is an emerging potential TMS target in bipolar disorder that may provide mood stabilization. This region may be targeted in this study if an anti-manic response to the previously mentioned DLPFC target is not observed. Baseline and immediate-post YMRS scores will be used to measure anti-manic response. Participants will be treated with 1,800 pulses of iTBS (3-pulse 50-Hz bursts at 5-Hz for 2-second trains, with trains every 10 seconds) per session at 90% resting motor threshold and depth-adjustment to the MNI target (Nahas *et al.*, 2004). Each session will last 10 min followed by a 50-minute intersession interval. Ten sessions will be applied per day (18,000 pulses/day) for 5 consecutive days (90,000 total pulses).

Dosing and administration: We will deliver only active aiTBS intervention via a MagPro X100 (MagVenture, Skovlunde, Denmark) TMS. The intervention paradigm consists of 10 daily sessions (50 total over 5 days) of intermittent theta-burst (iTBS) stimulation (3-pulse 50-Hz bursts at 5-Hz for 2-second trains, with trains every 10 seconds), delivered with 50-minute inter-session intervals (10-minute sessions, 50-minutes in between sessions). Stimulation will be delivered at 90% of the resting motor threshold (with depth correction to account for the distance between the scalp and cortex). aiTBS
protocol will be administered with a consistent dose escalation across all subjects of 18,000 pulses/day and 90,000 pulses/course. If participants meet remission criteria before treatment day 5 as measured by daily YMRS, participants will not receive further treatments.

The right DLPFC will serve as the target for stimulation, though DMPFC may also be targeted if this initial target does not demonstrate efficacy. The intervention target will be located via a Localite TMS Navigator. The treater identifies the target in the manner approved by the FDA for the Localite TMS Navigator device.

Study Schedule:

Assessment	**Visit 1** **Screening**	**Visit 2*** **Baseline**	**Visit 3-7** **Treatment Days**	**Visit 8** **Immediate Post**
Capacity to Consent	x			
Screening Informed Consent	x			
Demographics	x			
MRI Safety Screening Form	x			

TASS	x			
Medical and Psychiatric History	x			
Urine Analysis	x			
Inclusion/Exclusion Criteria	x			
MINI	x			
SCID Overview	x			
MSSI	x			
YMRS**		x	x	x
BPRS		x	x	x
CGI		x	x	x
ASRM		x	x	x
MADRS-S		x	x	x

Current Medications		x	x	x
Motor Threshold		x	x	
Enrollment/ Randomization		x		
Adverse Events			x	x

Procedures	**Visit 1 Screening**	**Visit 2 Baseline**	**Visits 3-7 Treatment Days**	**Visit 8 Immediate Post**
Obtain MT	x	x	x	
Stimulation log (rTMS)			x	
Resting EEG		x		x
TMS-EEG		x		x
T1 MRI		x		x
Resting state fMRI		x		x
HRV		x	x	x

*for this inpatient TMS study, the screening and baseline visits could occur at the same time and place if the potential participant qualifies for the study

**A YMRS score of ≥12 is an inclusion criteria for this study. If this score falls below 12 after the participant has been enrolled then the YMRS score will be measured every third treatment, as opposed to once per day, for closer monitoring of manic symptoms. If the YMRS score falls below 7, this will be recorded as remission and the TMS treatment will end.

Adverse Event Reporting:

The occurrence of an adverse event (AE) or serious adverse event (SAE) may occur during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate electronic case report form (eCRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study psychiatrist will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, study staff will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

	Number of participants reporting each adverse event (%)*	
	10 Hz rTMS group (n=204)	iTBS group (n=208)
Headache	131 (64%)	136 (65%)
Nausea	22 (11%)	14 (7%)
Dizziness	8 (4%)	18 (9%)
Unrelated medical problem†	47 (23%)	46 (22%)
Fatigue	14 (7%)	16 (8%)
Insomnia	14 (7%)	10 (5%)
Anxiety or agitation	8 (4%)	9 (4%)
Back or neck pain	7 (3%)	6 (3%)
Unrelated accidents	2 (1%)	3 (1%)
Vomiting	1 (<1%)	1 (<1%)
Tinnitus	1 (<1%)	3 (1%)
Migraine aura	3 (1%)	4 (2%)
Abnormal sensations	2 (1%)	4 (2%)

rTMS=repetitive transcranial magnetic stimulation. iTBS=intermittent theta burst stimulation. *p>0·05 on Fisher's exact tests for each pair of proportions. †Predominantly common infections such as colds and flus.

Table 3: **Adverse events**

AEs will be systematically assessed at the start and end of every study day and will be assessed via the following standardized questions that will be asked by research staff:

- Have you had any difficulty with the study interventions?
- Have you had any problems or other things bothering you since our last visit?
- Has anything bothered you enough to...
    - ...prevent you from doing anything you had planned?
    - ...take a prescription or over-the-counter medication or supplement?
    - ...see a medical professional?
    - ...modify the treatment of a pre-existing medical condition?

Any positive response(s) to the above questions will be documented electronically as part of an AE form on REDCap. Any documented AE will be asked about at each subsequent AE assessment until it resolves or through the time frame specified above. In Table 3 above, there is a list of common AEs (Blumberger *et al.*, 2018). If an unexpected AE occurs, or if a common AE occurs with severity greater than that expected, the participant will be further evaluated by a member of the study team with formal medical training.

In addition, although the risk of TMS-induced mania is low (Tee and Au, 2020), it will be monitored using the YMRS scale as a solicited event. The scale will be administered at baseline, before each treatment day, and the immediate-post visit. The score will be monitored along with input from the inpatient clinical team concerning possible worsening of symptoms.

Research staff will be trained to attend to signs of AEs and to report any potential unrelated or unexpected AE immediately to the Protocol Director (PD) Jean-Marie Batail. If AEs occur, appropriate medical and/or

psychiatric care will be facilitated for the research participant, and recorded in the appropriate electronic AE logs on REDCap. As per Stanford IRB requirements, AEs will be reported to the IRB annually. The NIMH Program Officer will be informed of any actions taken by the IRB as a result of any AEs within 7 business days of notification by the IRB (e.g. study modifications imposed by the IRB).

All subjects will have telephone and email contact information to reach the Principal Investigator and the Stanford IRB, in case of any distress or adverse response to rTMS or other components of the study.

An AE or SAE can occur from the time that the subject signs the informed consent form to 7 and 30 days, respectively, from the time the subject signed the consent form regardless of relationship to the protocol or TMS device. All AEs and SAEs will be recorded on the subject-specific and study wide eCRFs. Signs and symptoms will be recorded using standard medical terminology.

The following AE information will be included (when applicable): the specific condition or event and direction of change; whether the condition was preexisting (i.e., an acute condition present at the start of the study or history of a chronic condition) and, if so, whether it has worsened (e.g., in severity and/or frequency); the dates and times of occurrence; severity; causal relationship to the TMS device; action taken; and outcome.

Serious adverse event reporting: The PI or his designee will immediately report to the IRB any serious adverse event (SAE), whether or not considered study intervention related, including those listed in the protocol or investigator brochure, and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event. In that case, the investigator will immediately report the event to the IRB.

All SAEs will be followed until satisfactory resolution or until the site investigator deems either the event is chronic or the participant is stable. Other supporting documentation of the event may be requested by the IRB and should be provided as soon as possible.

In case of SAEs, the study investigator will complete an Unanticipated Serious Adverse Event Form and submit to the IRB as soon as possible, but no later than 10 working days after the investigator first learns of the event. The Investigator will provide all relevant documentation pertaining to an SAE (e.g., additional laboratory tests, consultation reports, discharge summaries, postmortem reports, etc.) to the IRB in a timely manner. Reports relative to the subject's subsequent course will be submitted to the IRB until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

Designated study staff will be responsible for ensuring that unanticipated problems are reported to the IRB in compliance with their requirements for reporting serious and unexpected adverse events. Reporting will be conducted in compliance with guidelines specified by the Stanford University Research Compliance Office.

Statistical Analysis Plan:

Descriptive Statistics: Categorical data will be presented as percentages. Continuous data will be presented as means with standard deviations.

Inferential tests: Statistical significance will be set at $p<0.05$, two-tailed.

Covariates: Baseline demographic and clinical measures will be compared across intervention groups using standard statistical methods (i.e., categorical variables compared using Pearson chi square test of independence; continuous variables compared using univariate ANOVAs). Characteristics that display imbalance at the baseline measure or an association with the dependent variable will be assessed for inclusion as covariates in the final models.

Assumption checks: Continuous data will be analyzed using standard linear mixed-effects modeling in line with intent to treat analysis principles. If residuals of the standard linear models are non-normally distributed (Shapiro-Wilk), then data will be analyzed with generalized linear mixed models with Satterthwaite approximation of degrees of freedom and robust estimation of coefficients to handle violations of model assumptions. Autoregressive covariance structure will be used for all analyses except for cases in which the models fail to converge or converge on non-real solutions. In these cases, alternate covariance structures will be explored until the models converge on real solutions. All post-hoc pairwise comparisons will be Bonferroni-corrected for multiple comparisons.

General approach considerations: Primary analysis models will be reported both unadjusted and adjusted for significant clinical covariates. All statistical analysis will be conducted using SAS/STAT version 9.4 (SAS Institute Inc. 2015. SAS® 9.4 Statements: Reference, Fourth Edition. Cary, NC: SAS Institute Inc.). All statistical analyses will be overseen by our biostatistician Dr. Booil Jo, an associate professor in the Stanford department of psychiatry and behavioral sciences - Center for Interdisciplinary Brain Sciences Research. Dr. Jo holds a PhD in Applied Statistics from UCLA and is a leading expert in statistical analysis of mental health research.

Primary Objective: To determine the safety and tolerability of open-label aiTBS in inpatients with bipolar disorder I and II as measured by AEs and study retention rates.

Primary hypothesis: Open-label aiTBS will demonstrate high safety and tolerability in psychiatric inpatients experiencing acute manic symptoms with no SAEs reported and a study retention rate of greater than 90% of anticipated recruitment.

Informed Consent Process:

Consent and other informational documents provided to the participant: Consent forms describing in detail the study intervention, study procedures, and risks will be given to all participants. Written documentation of informed consent is required prior to starting assessments and study interventions. The following consent materials are submitted with this protocol:

Two signed consent forms will be obtained from each participant: (1) Screening consent form and (2) Study consent form. These consent forms will be administered electronically using REDCap and with a physical copy given to the participant.

Consent procedures and documentation: Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The study PI or his designee will explain the research study to the participant and answer any questions that may arise in a private setting. A verbal explanation will be provided in English of the purposes, procedures, and potential risks of the study and of the rights of a research participant. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants will be informed that participation is voluntary, and that they may withdraw from the study at any time without interruption to their care. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Consenting Processes: There will be two consent forms: one consent for screening procedures, and the other for study and enrollment procedures. For the first consent process, the clinical research coordinator (CRC) will screen the participant's eligibility for enrollment in the study. The study PI or physician or their designee will consent the participants for the second in-person phase of the consenting process, which involves discussing the risks of rTMS and MRI scanning. The participant will be consented in the sequence that has been defined by our protocol.

Education and Informed Consent Process: Consent forms will be Institutional Review Board (IRB)-approved, and the participant will be asked to read and review the document. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The signature will be electronically obtained as described above. The consent process will start with an introductory paragraph that describes the study. This statement will be followed by a description of the purpose of the research. The participant will be informed that this is an open-label study in which they will certainly receive active treatment. Next, the duration of the study and the procedures involved will be described.

The participant will be notified of the discomforts and risks along with the potential benefits. The participant will be notified as to the costs for participation (none) as well as the compensation (none) for participation. The participant will be made aware of the research funding source (The Baszucki Brain Research Fund). The participant will be given information regarding the fact that their participation is voluntary. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The participant will be made aware of alternative options. The participant will then be given contact information for asking questions about the study or voicing any potential concerns. The participant will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participant will have the opportunity to discuss the study with his or her family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. All participants will be provided a copy of their signed consent forms.

Finally, after reading the experimental subjects' bill of rights, the participant will be asked for their signature in order to consent and give permission to be in the research study. To ensure the participant

has capacity to consent, as part of this process the study psychiatrist or their designee will complete a Capacity to Consent form before the consent form is signed.

Plan for Review of Consent Document: The signed consent document will be confirmed by the PI or study psychiatrist or their designee and will be rechecked by the CRC(s) assigned to this study.

Documentation of Signed Consent: The *Site Screening and Enrollment Logs* will be utilized to record the consent and screening of all subjects and the outcome of each screening. These logs will provide a comprehensive list of all subjects who were screened for eligibility and all participants who enrolled into the study. This information will be maintained in our electronic study binder on Stanford Medicine Box and electronically in REDCap. All subjects who have consented and screened will be included in this log, including screen failures. Subjects will be tracked separately on logs, arranged by their screening or enrollment ID number. Each page will be numbered and maintained in these logs in the *Study Screening Binder* and the *Study Enrollment Binder*, respectively.

Risk/Benefit:

Given the high degree of safety of rTMS (Rossi *et al.*, 2009, 2021), there is a low risk-benefit ratio for this intervention. That is, the risks are low and potential benefits are high. rTMS will be performed and monitored according to widely accepted principles that maximize safety (Rossi *et al.*, 2009). Based on our previous open-label studies (Williams *et al.*, 2018; Cole *et al.*, 2020), many of the research participants who receive active aiTBS are likely to achieve rapid improvements in their psychiatric symptoms, with associated improvement in their social and occupational functioning with minimal side-effects.

Furthermore, the information gained from this study will inform further optimization and personalization of TMS therapy for bipolar disorder I and II. Hence, we believe that the risks associated with this study are minimal compared to the knowledge gained.

Study Timeline:

The entire project is estimated to take approximately 24 months, broken down into 20 months of data collection and an additional 4 months of analysis.

The total duration for each participant from the time of baseline assessment to study completion is approximately 7 days.

Data Safety Monitoring:

Safety oversight will be under the direction of the Protocol Director, Bora Kim. All adverse events, protocol deviations and reportable information will be tracked on REDcap and reported to the IRB as required. Lab personnel will meet at least quarterly to assess safety and efficacy data.

References

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