Accelerated Intermittent Theta-Burst Stimulation for Depressive Symptoms

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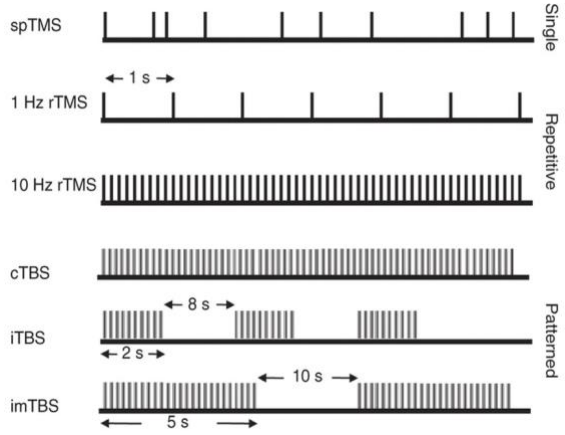
SPECIFIC AIMS

The overarching aim of this proposal is to test the preliminary efficacy of a highly efficient version of an established non-invasive neuromodulation technique, termed repetitive transcranial magnetic stimulation (rTMS). This novel technique, called accelerated intermittent theta-burst stimulation (aiTBS), is to be utilized as a rapid-acting intervention for depressive symptoms and suicidality. Excitatory rTMS over L LDPFC is FDA-approved for treatment-resistant depression (TRD). The onset of antidepressant response ranges between two to four weeks, which is not an optimal strategy for rapidly affecting acute depressive and suicidal thinking and behaviors. The aiTBS protocol suggested here may induce a faster onset of antidepressant effect by employing 10 sessions/day for 5 consecutive days (90,000 total pulses). This application is motivated by two recent findings in the neuromodulation field.

First, multiple sham-controlled investigations, evaluating an accelerated rTMS protocol, where multiple stimulation sessions were safely delivered across 2-5 days, demonstrate safety, tolerability, and efficacy of such stimulation. Importantly, this verifies that rTMS cannot only be 'accelerated,' safely and effectively, but it has demonstrated efficacy for depressive symptoms among both inpatient and outpatient samples. Relevant to the proposed study, and to high-risk target samples, these studies demonstrated significant post-stimulation reductions in acute depressive and suicidal symptoms.

Second, two landmark sham-controlled trials using a new, more powerful type of rTMS, intermittent theta-burst stimulation (iTBS), applied to the left dorsolateral prefrontal cortex (L-DLPFC), demonstrate strong efficacy (with large observed effects) among those with treatment-resistant depression (TRD), a condition where risk for suicide is considerably heightened. A single application of iTBS is shown to have 5X the potency of traditional high frequency rTMS, allowing for a much-reduced stimulation time in comparison to traditional rTMS, therefore making multiple stimulation sessions per day feasible. We thus propose novel evaluation of this low-risk brain stimulation intervention (i.e., capable of modulating neural circuitry that underlies self-preservation, cognitive control, and affective regulation), as an innovative approach for acute suicidal symptoms. This intervention will be investigated in the context of a randomized, two-site trial for indication as a rapid-acting rTMS intervention for acute depression and suicidal behaviors among high-risk psychiatric inpatients.



Taken from Dayan, Eran, et al. "Noninvasive brain stimulation: from physiology to network dynamics and back." Nature neuroscience 16.7 (2013): 838-844)

RAPID (5 DAY) TBS FOR ACUTE DEPRESSIVE AND SUICIDAL SYMPTOMS: A RANDOMIZED CONTROLLED TRIAL (N=200)

Within a two-site trial, we propose development and testing of an accelerated intermittent theta-burst stimulation (aiTBS) according to primary, secondary, and exploratory outcomes. Psychiatric inpatients will be randomized to one of two stimulation arms: (1) L DLPFC aiTBS –or- (2) ACC aiTBS.

Primary Aims Primary Outcome: Suicide Ideation (SI) Symptoms, Suicide Attempts (SA).

Aim 1.1: To develop and test the feasibility of a standardized L DLPFC and ACC aiTBS protocol for acute depressive and suicidal symptoms.

Aim 1.2: To examine the preliminary efficacy of aiTBS (both L DLPFC and ACC) in lowering suicidal ideation symptoms.

Hypothesis 1: Both L DLPFC and ACC aiTBS will result in significant reductions in SI symptoms and incident SA, but each target will produce a novel pattern of suicide symptom reductions.

Secondary Aims Secondary Outcome: Mood Indices (Depressive Symptoms, Emotion Regulation (ER) Deficits)

Aim 2: To examine indications of aiTBS (both L DLPFC and ACC) response in reducing targeted mood indices.

Hypothesis 2: Both L DLPFC and ACC aiTBS will result in significantly reduced depressive symptoms and ER deficits.

Exploratory Aims Exploratory Outcome: Symptoms specific to the patient's primary diagnosis

Aim 3: To explore whether symptoms associated with patients' primary diagnoses are also reduced as a consequence of aiTBS.

Hypothesis 3: In addition to the anti-depressant effects, both L DLPFC and ACC aiTBS will result in significant improvements in symptoms associated with primary diagnoses. Each stimulation site will result in a different pattern of symptom improvement.

BACKGROUND AND SIGNIFICANCE

Suicide represents a preventable problem, accounting for 57% of all violent deaths annually (Krug, Mercy, Dahlberg, & Zwi, 2002; Wong, 2003). In addition, an estimated 10 to 25 nonlethal attempts (100-200 for youth) occur for every death by suicide. Given its overwhelming public health significance, the prevention of suicide has been deemed a National Imperative (Wong, 2003). Despite high treatment demand among those at risk for suicide (i.e., half will refuse treatment, and 75% will drop out <1 year; Krulee & Hales, 1988; Rudd et al., 1996), the time required for therapeutic response to standard pharmacologic and psychotherapy treatments (i.e., weeks, months) is mismatched to the acute nature of a suicidal crisis. This highlights the alarming urgency and need for development of rapid-action therapeutic agents for suicidal behaviors.

At the level of the neural network, suicidality is theorized as a state of emotional dysregulation coupled with suboptimal cognitive control (Tracy et al., 2015). Dysfunctional neural circuits underlying cognitive control and affect regulation are proposed to underlie suicidal ideation and behavior. A non-invasive brain stimulation technique, termed rTMS, has been demonstrated to modulate the neural networks underlying cognitive control and affect regulation (Fox, Halko, Eldaief, & Pascual-Leone, 2012; Liston et al., 2014). By applying brief, high-intensity magnetic fields to the scalp (George, Taylor, & Short, 2013a), rTMS enables investigation and neuromodulation of the neural networks underlying specific subregions of interest (George et al., 2015). Two rTMS strategies have thus been suggested; turn down dysfunctional affective regulation or turn up cognitive control (Tracy et al., 2015). Both approaches may, however, be required to effectively modulate all neural networks involved in self-preservation and mood regulation processes (Nahas et al., 2010; Williams et al., 2016). The dorsolateral prefrontal cortex (DLPFC) is a core component of the cognitive control circuit (Lesh et al., 2013; MacDonald, 2000), this area is hypoactive in depressed patients (Grimm et al., 2008; Koenigs & Grafman, 2009) and DLPFC stimulation has been shown to reduce suicidal ideation (Desmyter et al., 2016; George et al., 2014). The anterior cingulate cortex (ACC) is an area associated with both cognitive control and affect regulation circuits. Reduced activity in ACC has been found in depressed patients during cognitive control tasks (Halari et al., 2009) and reduced ACC volume has also been reported in depressed patients (Ballmaier et al., 2004; Botteron, Raichle, Drevets, Heath, & Todd, 2002; Caetano et al., 2006). Suicidal ideation and behavior have been associated with differences in ACC functional connectivity (Chase et al., 2017; Du et al., 2017; Minzenberg et al., 2015). Therefore, both the DLPFC and the ACC are promising stimulation targets when probing the neurocircuitry underlying depressive symptoms.

Suicidal ideation and major depressive episodes are not symptoms which are restricted to clinical diagnoses of MDD; depressive symptoms and suicidal thoughts are experienced by patients with a range of psychiatric conditions. For example, individuals with diagnoses of bipolar disorder, schizophrenia, anorexia nervosa, opioid use and alcohol use disorder have been reported to have greater than 10 times higher risk of suicide than the general population (Chesney et al., 2014). rTMS has successfully induced antidepressant effects in individuals with a range of psychiatric diagnoses (J. C. Cole, Bernacki, Helmer, Pinninti, & O'Reardon, 2015; Desmyter et al., 2016; George et al., 2014; McClelland et al., 2013; Rosenberg et al., 2002). The proposed aiTBS protocol

could therefore potentially be effective at reducing depressive symptoms and suicidal ideation in patients with a range of primary psychiatric diagnoses.

Using a systems neuroscience approach (Williams et al., 2016a; 2016b), the current study thus proposes novel testing of an rTMS approach for its efficacy, while enabling study of transdiagnostic targets for suicide prevention. Recently, a specialized form of rTMS was developed, termed theta burst stimulation (TBS), which uses short, higher-frequency stimulation pulses (i.e., 50 Hz, every 200 ms; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005) to produce more robust effects on the brain region of interest. In the case of neuropsychiatric conditions, TBS has been demonstrated to modulate clinical mood assessments(Li et al., 2014) as well as neurocognitive performance (Demeter, Mirdamadi, Meehan, & Taylor, 2016). This approach is thought to more directly mimic the natural rhythms of the brain (Huang et al., 2005) and is unique insofar as the stimulation sessions required are significantly reduced (Daskalakis, 2014; George et al., 2010). For example, studies demonstrate equivalent antidepressant efficacy for 3 mins of TBS versus 37 mins of rTMS (Blumberger et al., 2015). Using an accelerated rTMS approach (i.e., stacking ten, 10-min sessions into 1 day, with spaced sessions), this method enables a reduction from 4-6 weeks of stimulation to only 5 days (i.e., or 500 total mins; Holtzheimer et al., 2010).
Important to the present study, the antidepressant effect of rTMS has been demonstrated across diverse populations (George et al., 2014; Li et al., 2014), samples (clinical, nonclinical; (Demeter et al., 2016), and psychiatric conditions (George et al., 2014; Hadley et al., 2011; Isserles et al., 2013; Li et al., 2014; Mallet et al., 2008), highlighting its trans-diagnostic utility and effectiveness. Findings furthermore suggest that rTMS/TBS is a safe(Hong et al., 2015) and efficacious, non-invasive treatment for depression (Li et al., 2014), which, likewise, produces minimal side effects in comparison with standard pharmacotherapies. Next, an accelerated rTMS approach, recently tested among psychiatric inpatients referred for imminent suicide risk, demonstrates its safety, feasibility, and preliminary efficacy for the proposed trial (George et al., 2014). Combined with a comprehensive assessment battery of proposed warning signs and biomarkers, this neuromodulatory approach has the ability to reveal testable hypotheses (Tracy et al., 2015) about suicidal behaviors, and their underlying neural circuitry, to inform mechanistic understanding of rTMS.

Innovation.

Suicide may be considered the tragic outcome of psychiatric illness and interacting risk factors. Our proposal aims are in accordance with the NIMH mission to advance understanding of the causes and prevention of suicide, particularly those, which promote evidence based prevention and treatment strategies. Commensurate with this goal, the current project aims to develop and test a new approach to the prevention of suicidal behaviors among psychiatric inpatients, utilizing a rapid-acting brain stimulation technique aimed at modulating the neurocircuitry underlying suicidal ideation. This goal is furthermore aligned with the Research Domain Criteria (RDoC) NIMH strategic aims (Insel et al., 2010) to examine mechanisms of psychopathology using a broad-based, multi-dimensional approach, emphasizing neurobiological assessment and developmental trajectories. Using a systems neuroscience approach (Williams et al., 2016a; 2016b), novel testing of a rapid-action intervention for suicidal behaviors enables theoretically-driven study of neural networks underlying antidepressant responses. The proposed study may also represent an innovative approach clinically.

First, we are proposing a low-risk intervention (Hong et al., 2015) that targets a high-risk sample for which retention in treatment is alarmingly poor. Testing use of non-invasive brain stimulation may be an effective strategy to enhance access to care. Second, suicide risk is a clinically-distinct taxon (Witte, Holm-Denoma, Zuromski, Gauthier, & Ruscio, 2017), which exists across diverse medical conditions. An intervention that targets neural circuitry underlying neurocognitive and affective deficits, that lie at the intersection of suicidal behaviors, promises insights into the pathogenesis of risk. Third, the proposed project allows us to evaluate whether a non-suicide focused intervention, targeting dysfunctional brain circuits, is more acceptable to participants. In this way, the proposed intervention may be valuable as a stand-alone or adjunctive to standard treatment, or as a means to improve retention. Fourth, brain-based interventions may be less stigmatizing compared to suicide-focused interventions. Testing use of a non-mental health intervention may be an effective tactic to enhance acceptance of care. Fifth, the time to psychotherapy and pharmacological treatment response remains mismatched to the acute nature of a suicidal crisis. By comparison, the brevity of aiTBS may increase accessibility and ease of intervention among an otherwise low-treatment seeking, high-need group (Nock et al., 2013). Sixth, suicide is preventable, yet research-tested interventions are scarce (Christensen, Cuijpers, & Reynolds, 2016; Mann et al., 2005).

The proposed study thus has public health significance and addresses a gap in the literature wherein efficacious interventions are either few in number, unacceptable to patients (i.e., based on retention rates), or inaccessible to those most in need.

Preliminary Studies.

The preliminary studies below support feasibility of the proposed trial.

George et al. (2014).Brain stimul; 7(3):421-431.
Conducted randomized, sham controlled trial of N=42 suicidal inpatients (n=17 post traumatic stress disorder (PTSD), n=23 mild traumatic brain injury (mTBI) and PTSD) of 10 Hz rTMS targeting the L-DLPFC (3x/day across 3days, 9 total sessions), supporting safety and feasibility of rTMS. SSI-C scores declined (by 75%) significantly for both groups.

Hadley et al. (2011). JofECT; 27:18-25
Among N=19 patients with treatment-resistant bipolar or unipolar depression in an uncontrolled trial, 10 Hz rTMS over the DLPFC was associated with significant posttreatment reductions in BDI (66%) and SSI-C (84.2%). Higher levels of rTMS were well-tolerated, safe, and effective.

Li et al. (2014). Brain; 137(7): 2088-2098.
In a randomized sham-controlled trial, researchers compared continuous and intermittent pulsed TBS treatments, and their combination (cTBS, iTBS, cTBS+iTBS). Compared to control, TBS over DLPFC among those with TRD (N = 200) resulted in significant post-treatment reductions in HAM-D. Large effects were observed for iTBS and cTBS+iTBS relative to control.

Cheng et al. (2016). Prog neuropsychoph; 66:35- 40.
Among N=60, a sham-controlled trial compared cTBS, iTBS, cTBS+iTBS (1x/day for 2 weeks) over DLPFC among those with TRD. Compared to control, iTBS showed superior improvements in HAM-D and on the WCST. Large effects were observed for iTBS compared to control.

Salomons et al. (2014). Neuropsychopharmacol; 39(2):488-498.
Among N=25 patients with unipolar and bipolar TRD, conducted 10 Hz rTMS (1x/day for 4 wks) with MRI neuronavigation. Treatment resulted in significant (45%) HAM-D reductions. Based on MRI, pretreatment sub-region connectivity (DMPFC, SGACC) predicts treatment response.

Bakker et al. (2014). Brain stimul; 8(2):208- 215.
Compared effects of 10 Hz rTMS (N = 98) and iTBS group (N=87; total N=185) on targeting the DMPFC (1x/day for 4 weeks). iTBS matched or exceeded the effectiveness of the 10Hz rTMS comparison on clinician and self-rated measures, and supporting safety and tolerability.

Downar et al. (2014). Biol psychiat; 76(3):176- 185.
Conducted DMPFC-rTMS using 10 Hz (1x/day for 4 wks) for unipolar or bipolar disorder patients with current treatment resistant depression (N=47). Patients showed statistically significant improvements on the HAM-D (51.1%) and the BDI-II (48.9%) from pre-treatment to post-treatment.

Clark et al. (2015). Curr Psychiatry Rep; 17:83

Based on review of rTMS use in PTSD (n=10 papers), with a focus on inpatient applications, both DLPFC and mPFC are implicated as an efficacious treatment target. rTMS proposed as a safe and well tolerated non-pharmacological intervention, warranting further investigation. In a sham-controlled trial conducted by George et al,[26] rTMS was administered to the L-DLPFC for 30 mins (3 x/daily) to N=42 psychiatric inpatients. Results revealed that rTMS produced rapid declines in SSI-assessed suicidal ideation. Compared to sham control, subjective ratings of 'being bothered by thoughts of suicide' likewise declined more with active versus sham rTMS. Findings were furthermore maintained at 3 and 6 months follow up. Comorbid conditions (PTSD, mTBI) were not excluded, and treatment was offered as an addition to TAU. Next, Li et al (Li et al., 2014) conducted a randomized, sham-controlled trial of intermittent theta-burst stimulation (iTBS) over DLPFC among N=60 participants with TRD. Relative to control, 2 weeks of daily TBS resulted in post-treatment reductions in depressive symptoms. Concurrently, rTMS has been demonstrated as efficacious when 'accelerated.'

Studies conducted by Hadley and colleagues (Hadley et al., 2011) and Holtzheimer and colleagues (Holtzheimer et al., 2010) support the safety, tolerability, and effectiveness of high dose rTMS antidepressant treatment protocols across treatment refractory samples, predicting post-treatment improvements in suicidal ideation and depression. Such studies support feasibility of the proposed trial.

Duprat et al. (2016) J Affect Disord; 200: 6-14

Randomized sham-controlled study investigating the effectiveness of aiTBS in patients (N=47) with treatment-resistant depression. Stimulation was applied to the left DLPFC at 110% resting motor threshold 5 times daily (1620 pulses per session) for 4 days. aiTBS to DLPFC was associated with significant reductions in the HAM-D compared to sham stimulation. aiTBS was well tolerated and safe, supporting the potential of aiTBS to DLPFC for quick and effective treatment of depressive symptoms in treatment-resistant depression.

Desmyter et al. (2016) Front Hum Neurosci; 10: 480

The effect of aiTBS on suicidal ideation was investigated in a subsample of patients from the trial presented by Duprat and colleagues above. aiTBS reduced the risk of suicide (BSI score) in previously treatment-resistant patients with depression who reported suicidal ideation prior to treatment (N=32). Reduced suicidal ideation was still present 1 month after baseline, 2 weeks after treatment had finished.

SIGNIFICANCE

Development of a rapid-acting stimulation protocol for psychiatric inpatients is motivated by scientific, clinical, and theoretical rationale. The crucial need for greater testing of interventions, likewise, remains mismatched to a dearth of trialists in suicide prevention. Indeed, clinicaltrials.gov search reveals that less than 10 clinical trials have been conducted, worldwide, evaluating suicide ideation and depressive symptoms as primary outcomes. In this way, investigation of a rapid, non-invasive neuromodulation intervention, among psychiatric inpatients, will address an important gap wherein few clinical trials exist, in particular those utilizing a biologically-based approach.

Rationale for Efficacy Testing Among Psychiatric Inpatients. Rationale for the use of a non-mental health intervention targeting high suicide risk psychiatric inpatients, is motivated by: (1) the high sustained rates of suicide across psychiatric inpatients, (2) the perceived stigma associated with mental health care treatment observed, (3) the correspondingly low rates of reported treatment seeking and retention, (4) the mismatch between the time course of therapeutic response to standard pharmacolocic and psychotherapy treatments and the imminent risk to suicidal patients, [5] preliminary data from rTMS and aiTBS trials (Cheng et al., 2016; George et al., 2014; Hadley et al., 2011; Li et al., 2014), conducted among psychiatric inpatients, demonstrating the safety, feasibility, and efficacy for depression, and (based on an rTMS pilot) suicidal symptoms specifically, (6) the planned use and integration of a transdiagnostic RDoC data sharing platform, with potential to synchronize NIH efforts to enhance prediction science by large-scale data capture and comparisons. Based on all such rationale, we propose study of an intervention targeting neural networks associated with depression and acute suicidal risk using a safe, low risk approach, with broad scientific and clinical impact. Finally, the proposed trial offers long-term application to prevention, with potential adaptation to military preventive strategies. Taken together, we propose testing of aiTBS as an innovative and low-risk intervention strategy to enhance suicide prevention among psychiatric inpatients.

Hypotheses and Technical Objectives. We aim to test the preliminary efficacy of a novel rapid-acting transdiagnostic brain-stimulation technique for acute depression and suicidal behaviors. The proposed study will combine two efficacious rTMS paradigms, accelerated rTMS (Baeken et al., 2015; Holtzheimer et al., 2010) and intermittent TBS (Chistyakov, Rubicsek, Kaplan, Zaaroor, & Klein, 2010; Daskalakis, 2014; Li et al., 2014) for initial testing, which we term accelerated theta-burst stimulation (aiTBS). We hypothesize that, aiTBS (both L DLPFC and ACC) will produce significant reductions in: (1) suicidal ideation and risk for suicide attempts (primary hypothesis), and (2) change in depressive symptomatology and emotion regulation function (Becker, Strohbach, & Rinck, 1999; Cha, Najmi, Park, Finn, & Nock, 2010; R. et al., 2013) (secondary hypothesis). We will also explore (3) change in symptomology associated with patient's primary diagnosis in patients who have a psychiatric diagnosis other than MDD and (4) mechanisms and moderators of antidepressant responses, including known behavioral, neurocognitive, and psychosocial variables for suicidal behaviors, based on past reports and NIH-funded research (Turvey et al., 2002).
Technical Objectives 1-2: Develop and Test an aiTBS Protocol for Suicidal Ideation Symptoms

1) Manualize a novel neuromodulation strategy for suicidal behaviors among psychiatric inpatients.

2) Examine aiTBS (both L DLPFC and ACC) efficacy in lowering suicidal ideation

Hypothesis 1: Both L DLPFC and ACC aiTBS will result in significantly lower SI symptoms and risk for SA.

Technical Objective 3: Evaluate Impact of Protocol on Targeted Secondary Measures of Mood

3) Examine aiTBS effects on reducing affective dysregulation indices.

Hypothesis 2: Both ACC and L DLPFC aiTBS will result in significant improvement in mood function, including depressive symptoms and affective regulation.

Technical Objective 4: Evaluate Impact of Protocol on Symptomology Associated with Patients' Primary Psychiatric Diagnosis

4) Examine aiTBS effects on reducing symptomology associated with patient's primary diagnosis.

Hypothesis 3: Both ACC and L DLPFC aiTBS will result in significant improvement in primary diagnosis symptomology.

Technical Objectives 5-6: Explore Mechanisms and Moderators of Antidepressant Response

5) Explore mechanisms and moderators of antidepressant responses, based on candidate risk factors and biomarkers.

6) Explore L DLPFC and ACC aiTBS effects on reducing objective measures of the neural network that underlies cognitive control and affective regulation.

Hypothesis 4: Genetic, microbiome and EEG biomarkers will be identified which significantly predict response to aiTBS.

Hypothesis 5: Both L DLPFC and ACC aiTBS will increase measures of cognitive control circuit and affective regulation circuit connectivity.

RESEARCH DESIGN AND METHODS

Participants. We propose preliminary testing of an aiTBS protocol for suicidal behaviors among psychiatric inpatients. Participants (N=200) will be recruited according to study inclusion/exclusion criteria using an established, in-use protocol of high suicide risk psychiatric inpatients (NCT01958541). To protect the safety of the target sample, this intervention will augment TAU by providing evidence-based suicide risk assessment and safety planning (Mann et al., 2005). The stimulation protocol will consist of 5 days of intensive (500 mins) TBS.

Targeted Brain and Affective Circuits. Two primary circuits are proposed as targets for stimulation to inform the pathophysiology of effect on primary, secondary, and exploratory outcomes. This includes: (1) The "Negative Affect" circuit, and (2) the "Cognitive Control" circuit. The negative affect circuit is engaged by negatively-valenced stimuli and comprises subcortical nodes in the amygdala, brainstem, hippocampus and insula, and prefrontal nodes. This includes the dorsal medial prefrontal cortex (DMPFC) and dorsal ACC connections, as well as ventral mPFC (vMPFC) and ventral-rostral ACC connections (Kober et al., 2008; Robinson et al., 2014). Whereas dorsal/rostral nodes have been preferentially implicated in appraisal, in which expression of emotion may be considered an "aversive amplification" sub-network (Robinson et al., 2014); ventral nodes are implicated in automatic regulation of negative emotion (Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010; Kober et al., 2008). These sub-networks may be engaged, even in the absence of conscious sensory awareness, via direct brainstem inputs (Kober et al., 2008; Williams, 2006). Given their commonly observed co-activation (Kober et al., 2008), the negative affect circuit could subserve the perception of negative emotion, and arousal aspects of feeling these emotions. The cognitive control circuit comprises the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), dorsal parietal cortex (DPC) and pre-central gyrus (Williams et al., 2016). Together, these regions, and their interconnectivity, are implicated in working memory and selective attention (Niendam et al., 2012), (evidenced by convergent neuroimaging methods; Cole & Schneider, 2007). Under task-specific demands, the cognitive control circuit is implicated in cognitive flexibility (Roalf et al., 2014). In the proposed study, we treat such circuits as independent (vs. dependent) variables to parse out neural factors in a trans-diagnostic manner, conceptualizing extremes along dimensions of dysfunction and underlying brain circuits.

Neuromodulation. The proposed intervention will target the left dorsolateral prefrontal cortex (L-DLPFC) and the bilateral anterior cingulate cortices (bil ACC). The DLPFC (BA 9 and 46; (Cieslik et al., 2013)) is a critical node in the mesocortical system (central to the proposed Cognitive Control circuit), a dopaminergic tract that modulates anticipation, goal selection, planning monitoring, and the use of feedback in task performance (Bonelli & Cummings, 2007). The DLPFC is also critical for working memory of spatial and non-spatial information (Fuster, 2015). There has been some suggestion that direct stimulation (activation) of the cognitive control network (CCN) modulates the connected parietal attentional networks involved in the automatic processing of environmental stimuli. According to recent meta-analysis (of 162 imaging studies), coactivation of BA 9 (which spans dorsolateral and medial prefrontal cortices) and midbrain regions (e.g., periaqueductal gray or PAG) is essential for assigning emotional valence (Kober et al., 2008). These results underscore the critical role of this region in mood regulation (Lévesque et al., 2003). In depressed patients, the

L-DLPFC is hypoactive and thought to be associated with negative emotional judgment; as a result, it has constituted a primary rTMS target for depression (George, Taylor, & Short, 2013). Previous studies of rTMS for suicidality have likewise targeted L-DLPFC, showing safety, feasibility, and therapeutic benefit (Desmyter, Duprat, Baeken, Bijttebier, & Van Heeringen, 2014; George et al., 2014). The ACC is involved in emotion regulation and has also been found to be hypoactive in depressed patients (Halari et al., 2009). rTMS has been applied to ACC in patients with OCD and MDD, producing reduced depressive symptoms and highlighting safety and tolerability of the technique (Kreuzer et al., 2015; Vanneste, Ost, Langguth, & de Ridder, 2014; Zangen et al., 2016). Cognitive Control and Negative Affect circuits have been shown to interact in the explicit/implicit regulation of emotion (Bernert et al., 2013; Lee & Siegle, 2012; Ochsner & Gross, 2005) . Additionally, following rTMS to the DLPFC, ACC grey matter has been shown to increase and the degree to which this occurs, correlates with improved depressive symptoms (Lan, Chhetry, Liston, Mann, & Dubin, 2016). This highlights the rationale for testing a brain stimulation protocol which targets both circuits implicated, to optimize antidepressant responses (Bakker et al., 2015; Downar, Blumberger, & Daskalakis, 2016; George et al., 2010). The protocol will be standardized, and tested at two stimulation sites for efficacy in the prevention of suicidal behaviors. Eligible psychiatric inpatients will be randomized to one of two conditions, (1) L DLPFC aiTBS or (2) ACC aiTBS.

Eligibility. Screening will use a structured diagnostic interview [Mini International Neuropsychiatric Interview; MINI], self-report inventories, and clinician-administered scales to determine study eligibility. Rather than occurring exclusively in the context of depression, suicidal symptoms exist across Axis I psychiatric diagnoses; therefore, we will include patients with primary diagnoses other than major depressive disorder (MDD) if they display suicidal ideation or are experiencing a major depressive episode. Previous rTMS and TBS trials, which have evaluated benefit to suicidal ideation and depressive symptoms, have been conducted among those with diverse comorbid psychiatric and medical conditions (e.g., PTSD(Berlim & Van Den Eynde, 2014) OCD (Dunlop et al., 2016), TBI (George et al., 2014), etc.), and among those on concurrent medications(George et al., 2014; Levkovitz et al., 2015). Participants will not be asked to change or discontinue medications as a condition for participation in this study, and current pharmacotherapy or psychotherapy will not be a basis for exclusion provided that changes do not immediately precede enrollment.

Inclusion criteria:

1. Over 18 at the time of screening

2. Able to read, understand, and provide written, dated informed consent prior to screening. Participants will be deemed likely to comply with study protocol and communicate with study personnel about adverse events and other clinically important information.

3. Currently diagnosed with Major Depressive Disorder (MDD), according to the criteria defined in the Diagnosis and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)

4. Display suicidal ideation (score >6 on the SSI).

5. Meet the threshold on the total HAMD17 score of >/=20 at baseline.

6. Meet the threshold on the BDI-II score of >/=17 at baseline.

7. Not in a current state of mania (Young Mania Rating Scale) or psychosis (MINI)

8. In good general health, as ascertained by medical history.

9. Access to clinical rTMS after hospital discharge

Exclusion criteria:

1. Any structural lesion e.g. structural neurological condition, more subcortical lesions than would be expected for age, stroke effecting stimulated area or connected areas or any other clinically significant abnormality that might affect safety, study participation, or confound interpretation of study results.

2. Metal implant in brain (e.g. deep brain stimulation), cardiac pacemaker, or cochlear

3. History of epilepsy/ seizures (including history of withdrawal/ provoked seizures)

4. Shrapnel or any ferromagnetic item in the head

5. Pregnancy

6. Autism Spectrum disorder

7. Any current or past history of any physical condition which in the investigator's opinion might put the subject at risk or interfere with study results interpretation

8. Active substance use (<1 week) or intoxication verified by toxicology screen--of cocaine, amphetamines, benzodiazepines

9. Cognitive impairment (including dementia)

10. Current severe insomnia (must sleep a minimum of 5 hours the night before stimulation)

11. Current mania or psychosis

12. Showing symptoms of withdrawal from alcohol or benzodiazepines

13. IQ<70

14. Parkinsonism or other movement d/o determined by PI to interfere with treatment

15. Desirous of getting ECT and previous tolerant exposure to ECT

16. Any other indication the PI feels would comprise data.

17. No access to clinical rTMS after discharge

STIMULATION

Accelerated theta-burst stimulation (aiTBS) Brainsway TMS Platform. The TMS stimulator (Brainsway H-Coil, Israel) will be used to generate repetitive biphasic magnetic pulses. Both stimulation groups (ACC aiTBS and DLPFC aiTBS) will receive simulation from specially-designed coils (Brainsway H-Coil, Israel). The ACC stimulation utilizes the H7 coil and the L DLPFC stimulation utilizes the H1 coil. We will employ a spaced intermittent theta-burst technique (Goldsworthy, Pitcher, & Ridding, 2012) capable of modulating targeted brain region of interest, L-DLPFC (Duprat et al., 2016) and ACC.

Stimulation Timing, Dose and Spacing: This study will utilize a total of 50 applications of 1800 pulses of iTBS at 90% of the resting MT; proven effective in producing a prolonged change in cortical excitability(Huang et al., 2005). The (50-min) spaced application of TBS was chosen as the stimulation strategy given its ability to produce sustained effects to the targeted neural network. By comparison, research suggests that continuous stimulation approaches (without spacing) can minimize or reverse intended effect (Gamboa, Antal, Moliadze, & Paulus, 2010). Such spacing has been tested for safety and specificity of achieved stimulation targets in animal and human models (Larson & Munkácsy, 2015). This TBS approach will be applied to L-DLPFC or ACC (randomized). Dosing of aiTBS will = 90% of the active MT adjusted to the skull to cortex distance, as this is documented to modulate the desired cortical target (Huang et al., 2005; Li et al., 2014). 1800 pulses of iTBS at 50 Hz will be utilized, consistent with standard parameters. There will be 10 trains of 3 pulses at 50Hz every 200ms (50Hz over 5Hz), which is 30 pulses per theta burst train. 60 trains will be delivered to achieve 1800 pulses. This will utilize 10 stimulation sessions of 1800 pulses (with 50-min spacing between each iTBS session; Duprat et al., 2016)). This will generate a 10 total stimulation sessions/day, 50 sessions total over the 5 days with a total of 90,000 pulses.

Motor Threshold (MT) Elicitation: Inherent to the safe and accurate dosing of TBS stimulation, active MT elicitation will be performed according to established protocols, which have been in use since 1994 (George et al., 2010; Pascual-Leone, Valls-Solé, Wassermann, & Hallett, 1994). This protocol is well-established as an effective method for MT Elicitation (Borckardt, Nahas, Koola, & George, 2006), widely implemented within both sham-controlled rTMS and TBS trials with demonstrated safety (Borckardt et al., 2006; George et al., 2013b).

Potential Risks: rTMS is FDA approved as a non-invasive treatment modality for depression (George et al., 2013b). There is no known risk of seizure for the above-stated brain stimulation parameters (Huang et al., 2005; L. Oberman, Edwards, Eldaief, & Pascual-Leone, 2011). The MT is reflective of stimulation output necessary to cause neuronal depolarization. Since its first use in 2005 (Huang et al., 2005), only one case of TBS has resulted in seizure, which occurred for stimulation at >100% resting MT (120% of aMT) and this was cTBS not iTBS (L. Oberman et al.,

2011; L. M. Oberman & Pascual-Leone, 2009). Finally, the proposed stimulation parameters mirror those used in Stanford IRB-approved TBS protocols underway (Protocol Director Williams N; ID 33797, ID 38138), which have received a "minimal risk" designation. Further, studies utilizing 90% rMT are shown to modulate a deep target as has been validated in the motor system (Mori et al., 2010), suggesting that past parameters are safe (Nathan Bakker et al., 2015), yet may be further optimized (Mori et al., 2010).

STIMULATION RESPONSE, INTEGRITY, AND TRAINING

Evaluation of Response. Response to aiTBS will be quantified by the reduction in score on SSI-C from baseline to post-aiTBS. The primary clinical endpoint for outcome will occur at Day 6 (after the aiTBS course, after the participant has slept).
Responders will be defined as individuals who show 50% decrease in SSI-C as the result of 5 days of aiTBS. The effect of aiTBS on depressive symptoms (HAMD-24) and symptoms associated with patients' primary diagnosis will be quantified in the same way.

Participant Acceptance and Focus Groups. Dropout following baseline assessment will operationally define acceptance. This definition will be used to guide intent-to-treat analyses. Study completers and non-completers will be invited to focus groups to elicit feedback about: (a) reaction to aiTBS format/timing, (b) attitudes/ expectations toward aiTBS, (c) ease of participation, (d) perceived barriers, and (e) aiTBS satisfaction. With consent, these will be recorded and transcribed for review. All data will be reviewed and applied to protocol refinements.

NIH toolbox: Cognitive abilities will be tested before and after the aiTBS course using a number of neurocognitive assessments that are accessed through the NIH toolbox ipad app. The assessments will provide measures of executive function, attention, working memory, episodic memory and processing speed. Measuring cognitive abilities of participants before and after aiTBS will allow us to demonstrate the safety of the technique in terms of cognitive effects as well as identify potential cognitive improvements associated with antidepressant responses.

EEG measures:
Resting-state electroencephalography (EEG) will be recorded before the first aiTBS session and after the final session, to monitor changes in brain activity and functional connectivity as a result of aiTBS. Baseline EEG recordings will also be used to identify potential indicators of aiTBS response. EEG measures will also be taken during stimulation sessions to identify aiTBS-induced changes in brain activity.

MEASURES AND MATERIALS

Eligibility and Screening Measures

Antidepressant Treatment History Form [ATHF; Fava, 2003)]: This is an established, clinician-administered tool to assess history of treatment non-response according to standard criteria within clinical trials.

Maudsley Refractoriness Measure [MRM; Fekadu, Wooderson, Markopoulo, et al., 2009a; 2009b)]: This uses a staging model to provide a continuous index of treatment refractoriness, found to have strong predictive utility and sensitivity to treatment response.

TMS Adult Safety Screen [TASS]: This self-report instrument assesses risk of seizure related to TMS. Any identified risk will disqualify the participant to minimize risk and ensure safety.

Mini International Neuropsychiatric Interview [MINI; Lecrubier et al., 1997; Sheehan et al., 1998]: The MINI is a structured diagnostic interview which is used to screen for a number of psychiatric disorders. This tool will be used to identify any potential comorbid conditions.

Demographic Overview: A brief demographic overview will be administered at baseline to assess basic demographic and medical history characteristics. Mini-Mental State Examination [MMSE; Folstein, Folstein, & McHugh, 1975]. This is a brief, mental status examination, widely-used in research and past trials. Scores > 24 are generally indicative of normal mental status function.

Medication Monitoring Form [MMF]: A medication monitoring survey will be administered at the start of each day of aiTBS to closely monitor medication use and changes throughout enrollment.

Young Mania Rating Scale [YMRS; Young et al., 2004]: This is an 11-item clinician-administered scale used to measure symptoms of mania. Each item is scored from 0-4 with scores of 4 indicating the presence of more severe mania. Participants who are currently experiencing a manic episode will not be enrolled in the study. This scale will be used to monitor symptoms of mania each day they receive aiTBS to make sure manic symptoms have not arisen during study enrollment.

Scale for Suicide Ideation—Current [SSI-C; Beck, Kovacs, & Weissman, 1979]: This is a clinician-administered questionnaire used to assess the severity of suicidal ideation, with higher scores indicative of greater symptom severity. Patients must display elevated scores (>5) to be enrolled in the study. The scale has strong psychometric properties, and is widely used in randomized suicide prevention trials.

Scale for Suicide Ideation—Worst Point [SSI-W; Beck, Brown, Steer, Dahlsgaard, & Grisham, 1999]: This is a 19-item clinician-administered scale to assess worst point symptoms in a participant's life (0-38). The SSI-W predicts up to a 13-fold increased risk for suicide, and is thus widely-used in intervention research to identify a subgroup of at-risk patients.

Suicidality Outcome Measures

Scale for Suicide Ideation—Current [SSI-C]: This is a 19-item clinician-administered rating scale to assess the severity of suicidal ideation, with higher scores (0-38) indicative of greater symptom severity. The scale has strong psychometric properties, and is widely used in randomized suicide prevention trials.

Columbia-Suicide Severity Rating Scale [C-SRS; Posner et al., 2011]: Clinician administered questionnaire identifying the presence or absence of six suicidal thoughts or behaviors in the past month or since the last visit. Each 'yes' answer is scored as 1, meaning the maximum total score is 6.

Depression Outcome Measures

Quick Inventory Depressive Scale-Self Reported [QIDS-SR; Rush et al., 2003]: The QIDS-SR is a 16-item validated self-report instrument, designed to measure the severity of depressive symptoms for one week. Items are rated on a 0-3 scale, with higher scores (0-27) indicating greater severity.

Hamilton Depression Rating Scale 24-Item [HAMD-21; Hamilton, 1960]: This is a clinician rated scale which assesses 21 symptoms from either 0-2 or 0-4. Total scores are between 0 and 76, higher scores on this scale indicate greater severity of depression

Montgomery-Asberg Depression Scale [MADRS; (Montgomery & Asberg, 1979)]This is a ten-item clinician rated questionnaire in which the clinician rates each item from 0-6. Scores of 6 indicate more severe depressive symptoms. Total scores are between 0 and 60 with scores>35 indicating severe depression.

Emotional Conflict Task [ECT; (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006)]: This is a brief, computerized task of implicit emotion regulation (ER). It consists of 148 presentations of happy or fearful facial expression photographs, overlaid with words "FEAR" or "HAPPY." Stimuli are presented (Neurobehavioral Systems, http://nbs.neuro-bs.com), and counterbalanced across trials for expression, word, response button, and gender. Subjects indicate facial affect with button press response. Deficits predict behavioral and neural correlates of psychopathology.

Difficulties in Emotion Regulation Scale [DERS; (Gratz, Roemer, Cameron, & Payne, 2011)]: This is a 36-item self-report instrument of explicit emotion regulation that has well-established reliability and validity, including in comparison with ECT.

Pittsburgh Insomnia Rating Scale-20 Item Version [PIRS-20; (Veqar, Moiz, & Hussain, 2014)]: A 20-item, self-report scale used to measure the quality of sleep an individual is getting. Total scores range from 0-60 with higher scores indicating a greater degree of sleep difficulty.

NIH toolbox (Weintraub et al., 2013): A number of neurocognitive assessments that are accessed through an ipad app. The assessments have been created by a team of 300 scientists from 100 academic institutions and have shown good psychometric properties (Heaton et al., 2014; Zelazo et al., 2014). The assessments provide measures of executive function, attention, working memory, episodic memory and processing speed.

Heart Rate Variability [HRV]: Individuals with depression tend to display lower levels of heart rate variability, reflecting atypical parasympathetic activity (Kemp et al., 2010). Heart rate variability will be measured each day during the aiTBS course to monitor changes.

Cortisol Levels: Individuals with depression tend to display elevated levels of cortisol; a hormone which is released in response to stress (Herbert, 2013; Lindqvist, Isaksson, Lil-Träskman-Bendz, & Brundin, 2008). Salvia samples will be taken at baseline and post aiTBS to record changes in cortisol levels as a result of aiTBS.

Primary Diagnosis Outcome Measures

Clinical Monitoring Form [CMT; (Sachs, Guille, & McMurrich, 2002)]: This is a clinician filled form used to assess both depressive symptoms and symptoms of mania associated with bipolar disorder. Robust correlations have been found between CMT assessments and well-established mood scales such as HAMD, YMRS and MADRS (Sachs et al., 2002).

The Positive and Negative Syndrome Scale [PANSS]: The presence of positive and negative symptoms of schizophrenia are rated on a scale from 1 (absent) to 7 (extreme). Seven negative symptoms, seven positive symptoms and 16 general symptoms of schizophrenia are assessed. Total scores for positive and negative scales range from 7 to 49.

The Calgary Depression Scale for Schizophrenia [CDSS; Addington, Addington, & Maticka-Tyndale, 1993)]:
A nine-item questionnaire designed to assess depressive symptoms in patients with Schizophrenia. Each item is rated from 0 (absent) to 3 (severe), resulting in total scores ranging from 0 to 27.

Alcohol Craving Questionnaire, short form [ACQ-SF-NOW; (Singleton, 2000)]: This is a 12-item self-report questionnaire. For each question, a statement is given and the participant indicates how strongly they agree or disagree to each statement across a 7-point scale. This questionnaire will also be sufficiently adapted so that we have version for patients with opioid use disorders and psycho-active drug use disorders.

Obsessive Compulsive Drinking Scale [OCDS; (Anton, 2000)]: This is a 14-item multiple choice self-report questionnaire. Each question has 5 possible responses rated from 0-5, scores of 5 indicate more prominent obsessions and compulsions regarding alcohol intake. This questionnaire will also be adapted so it can be applied to other substance misuse disorders (opioids, psycho-active drugs etc.) according to the patient's primary diagnosis.

Young-Brown Obsessive Compulsive Scale Modified for Binge Eating [YBOCS-BE; (Deal, Wirth, Gasior, Herman, & McElroy, 2015)]: This is a clinician-administered assessment which assesses five core dimensions: time spent on symptoms, interference due to symptoms, distress due to symptoms, resistance against symptoms, and degree of control over symptoms across 10 questions. For each question a score is given between 0 and 4 with 4 indicating severe obsessions/compulsions associated with bingeing behavior.

Yale-Brown-Cornell Eating Disorder Scale [YBC-EDS; (Mazure, Halmi, & Sunday, 1994)]: A clinician-administered scale that is not restricted to questions regarding a particular eating disorder. The YBC-EDS consists of 19 items assessing severity of preoccupations, rituals, and motivation for change. Each item is scored from 0 to 4 with 4 indicating more severe symptoms.

Eating Disorder Examination Questionnaire [EDE-Q; (Berg, Peterson, Frazier, & Crow, 2012)]: This is a 28-item self-report questionnaire in which participants rate the number of times certain events have occurred or how severe eating disorder related thoughts have been over the last 28 days. Each response is scored from 0 to 6 with 6 indicating a greater number of occurrences or more protruding thoughts in the last 28 days.

Post-traumatic Stress Disorder Checklist-Civilian Version [PCL-C; (Wilkins, Lang, & Norman, 2011)]: This is a 17-item self-report questionnaire assessing the key symptoms associated with PTSD. For each question, the amount each symptom has effected the individual in the month is rated from 1-5, 5 being extremely effected.

Hamilton Anxiety Rating Scale (HAM-A; (Hamilton, 1959)): A clinician rated scale which assesses 14 symptoms of anxiety on a scale of 0-4, with 4 indicating more severe levels of anxiety.

Generalized Anxiety Disorder 7-item (GAD-7; (Terrill, Hartoonian, Beier, Salem, & Alschuler, 2015)) scale: A 7 item self-report questionnaire, rating how often symptoms of anxiety occur. Each question is rated from 0-4 with scores of 4 indicating anxiety symptoms occur more frequently.

Numeric Rating Scale (NRS) for Chronic Pain (National Institute of Clinical Studies, 2011): Self-reported pain scale where pain experienced in the last 24 hours (average & worst) and current pain are rated from 1-10. Scores of 10 indicating the worst possible pain imaginable.

Panic Disorder Severity Scale (PDSS; (Houck, Spiegel, Shear, & Rucci, 2002)): A 7-item self-report questionnaire in which the frequency and severity of panic attacks are measured. Each item is rated from 0 to 4 with 4 indicating severe impairment caused by panic attacks.

The Somatic Symptom Scale (SSS-8; (Gierk et al., 2014)): A self-report questionnaire in which the severity of eight symptoms over the last 7 days are rated. Each item is rated from 0-4 with a score of 4 indicating more severe symptoms. This tool has been shown to have good validity and reliability (Gierk et al., 2014)

EEG Outcome Measures

Resting-state EEG recordings will be made both before and after aiTBS in order to examine potential EEG biomarkers for antidepressant response as well as identify aiTBS-induced changes in EEG recordings. Oscillations in the theta and alpha frequency bands over frontal areas are of particular interest as these waveforms have been identified as possible biomarkers for suicidal ideation.

Sequence of Investigation: Patients will first consent to be screened for eligibility to take part in the study, potential participants will be screened for inclusion based on central eligibility and screening measures. If patients are eligible, they will provide informed consent before participating in the study. Participants will complete 5 days of aiTBS as well as follow-up assessments (1 day after aiTBS). Data will be collected according to clinician administered, computerized, and self-report measures.

Clinician administered: SSI-C assessments will be conducted by a clinician. Suicide risk will be evaluated, with on-call DSMP IRB-approved procedures in place.

MRI Outcome Measures

Magnetic Resonance imaging will be made both before the first treatment (baseline) and after 50 aiTBS treatments (post-treatment discharge). The baseline MRI scan is required to determine the cortical depth measurement which is used to determine the strength of the aiTBS treatment administered. The immediate post-treatment scan is conducted to examine potential MRI biomarkers for antidepressant response as well as identify aiTBS-induced changes in MRI imaging.

DESIGN AND PROCEDURES USED TO ACCOMPLISH SPECIFIC AIMS

Suicidality Aim 1.1: To develop and test an integrated aiTBS intervention protocol for suicidal behaviors.

Analyses: Descriptive-level analyses will be conducted to evaluate feasibility, acceptance, residual symptom change, adherence and retention rates, in addition to data collected from focus groups (i.e., assessing palatability of individual protocol modules, ease of participation, protocol compliance etc.), to inform future adaptation and refinements to the protocol. In addition, quantitative analyses will be used to assess the average length of stay of patients undergoing aiTBS in comparison to TAU to observe whether aiTBS results in reduced lengths of stay.

Suicidality Aim 1.2: To examine aiTBS response in lowering suicidal symptoms.

Hypothesis 1: Both L DLPFC and ACC aiTBS will significantly lower suicidal ideation.

Analyses: Continuous data will be analyzed using standard linear mixed-effects modeling in line with intent to treat analysis principles. A mixed-effects linear model with auto-regressive error structure will examine differences between stimulation sites with respect to rate of change (the slope of individual regression lines) in: (a) SSI-C scores, (b) SIS scores. Though SSI-C will serve as the primary outcome, self-reported
indices of response (BSS, VAS-SI) will also be examined. For the primary analysis, we will use a random slope model and estimate the group differences (ACC aiTBS vs. L DLPFC aiTBS) across 3 points (baseline; day 1, post aiTBS). To test Hypothesis 1, growth parameter estimates will be converted to antidepressant effect estimates for our clinical endpoint (i.e., Day 1 post aiTBS).

Depression Aim 1: To examine aiTBS response in reducing targeted mood indices post- aiTBS

Hypothesis 1: aiTBS will result in significant reductions in mood dysfunction.

Analyses: The same analytic strategy above will be used to examine differences between stimulation sites (L DLPFC aiTBS vs. ACC aiTBS) with respect to rate of change in: (a) QIDS-SR, (b) DERS, (c) ECT. Though these will serve as main outcomes, self-reported indices of response (BDI, VAS-MI) will also be examined. The model will estimate fixed effects to compare stimulation effects across the same 3 assessment points. To test Hypothesis 2, growth parameter estimates will be converted to effect estimates for our primary clinical endpoint (i.e., day 1 post-aiTBS).

Exploratory Aim 1: To explore the effect of aiTBS on symptoms associated with participant's primary diagnoses.

Analyses: The same analytic strategy above will be used to examine differences between stimulation sites (L DLPFC aiTBS vs. ACC aiTBS) with respect to rate of change in symptoms associated with primary diagnoses (OCDS, EDE-Q, PANSS, PDSS etc.)

Exploratory Aim 2: To explore mechanisms and moderators of aiTBS outcome.

Analyses: In the mixed effects modeling framework, we will explore a comprehensive battery of proposed risk factors, candidate biomarkers, and underlying neural circuitry in the prediction of antidepressant response. The rate of change (slope of individual regression lines) in indicated risk factors will be tested as potential mediators of proposed effect on SSI-C scores. The model will estimate fixed effects to compare stimulation effects across the same 3 assessment points. This will include all exploratory and proposed biomarkers. For testing candidate moderators, baseline symptoms, genetic factors, microbiome and potential EEG biomarkers will be entered into the model. For testing candidate mediators, intermediate variables (using the MacArthur Model) will be used.

SAMPLE SIZE AND POWER

For power estimation, we consistently used an alpha of .05, and two-tailed tests. Post-aiTBS (Day 1, post- aiTBS) assessment will represent the primary clinical endpoint for all power calculations. Our longitudinal analyses will be conducted fully utilizing data that will be collected across all time points (baseline, aiTBS (days 1-5), and post-aiTBS, which will inform clinical and exploratory analyses. Power estimation was conducted focusing on our primary end point at the end of aiTBS. Feasibility analyses (e.g., acceptance, adherence, focus group data) will be conducted based on descriptive-level statistics to guide future adaptations and refinements of the proposed aiTBS protocol.

Power to detect preliminary symptom change (depression symptom reduction) for Hypothesis 1 is based on ES estimates observed in (1) a previous RCT pilot rTMS for pre-treatment to post-treatment symptom change in HAMD, and (2) two sham-controlled TBS trials, utilizing a similar treatment approach, which demonstrated large effects for depressive symptoms (>d=1). Given this information, we used a somewhat conservative effect size of d=0.8 for our power estimation. Based on our prior studies, we assumed about 10% attrition by 1 mos post-treatment. Under this setting, with an n=200, the estimated power to detect between-subjects effects on SI (hypothetical---L DLPFC aiTBS vs. Sham) would be 0.82 (alpha=.05, two-sided). We are not powered to test non-inferiority between the two stimulation sites, but believe that an n=200 would provide the appropriate amount of data for a future blinded study power calculation.

Data and Safety Monitoring Plan (DSMP) and Risk Assessment Framework

All procedures will be closely supervised by this study's PIs and on-site Medical Monitor, Dr. Schatzberg.

DISSEMINATION AND IMPLEMENTATION PLAN

The findings in this study have strong potential to impact psychiatric inpatient care by providing the first rapid acting intervention for acute depressive symptoms and suicidal risk. As of now, there are no low-risk, non-invasive interventions that remedy the urgency of an acute suicidal crisis to achieve therapeutic benefit; the proposed randomized controlled trial would be the first in the world to apply aiTBS to combat depression and suicidal ideation in psychiatric inpatients. Given data sharing aspects of an RDoC approach, study findings promise insights into risk on a large-scale, offering unique, long-term, transdiagnostic comparisons that extend beyond efficacy findings of the proposed trial. Data will be analyzed for its feasibility, efficacy, and according to mechanisms of antidepressant response. Given translational benefit, and oversampling of underrepresented groups (e.g., women) at elevated suicide risk, this aims to maximize relevance of our findings to relevant groups. PI will work with Brainsway to further the knowledge of and access to aiTBS and studied effects. To accomplish this end, information about aiTBS study results will be presented to stakeholders based on their guidance, for broad impact and implementation.

PROCEDURES AND PRECAUTIONS IN THE PROTECTION OF HUMAN SUBJECTS

Data and Safety Monitoring Plan (DSMP) and Risk Assessment Framework

All procedures will be closely supervised by this study's PIs. Suicide risk assessment will be conducted using empirically-established risk categorizations (minimal, mild, moderate, severe, imminent) to routinize clinical decision-making and emergency referral procedures for suicidal behaviors. This study will utilize a comprehensive, in-built infrastructure and set of standard operating procedures that support safe conduct of the current trial. Clinical staff will be notified of inpatients that are believed to be at imminent risk of suicide.

Data and Safety Monitoring Board (DSMB)

As a further protection against risk, a DSMB will be formally constituted to: independently review, oversee, and monitor risk procedures for the proposed study. DSMB construction will be closely guided by the PI's supervision, and consultation with Investigators and Consultants. This DSMB will report to Stanford University IRB regarding study recruitment and adverse event (AE) reporting on a monthly basis. The DSMB will consist of individuals with the following expertise, nonaffiliated with the study: (1) An expert in suicidology, (2) A biostatistician with expertise in clinical trials, and (3) A patient advocate. During the proposed intervention, participants and their physicians will be instructed to report any intervention-emergent AEs or symptoms to study Personnel. Adverse events will be closely monitored and assessed. DSMB and Stanford IRB will be immediately advised if a participant reports a serious emerging condition or AE—independent of cause or relation to the intervention. In the rare case that an AE warrants evaluation by the ombuds/patient advocate, DSMB consensus will have power to determine appropriateness of a participant's continuing participation. Such decisions will be binding.

DATA AND SAFETY MONITORING PLAN (DSMP)

Training of Personnel in Suicide Risk Assessment:

1. All study personnel will complete extensive clinical training in suicide risk assessment practices, led by the PIs, safety monitor, and planned consultants. This team will meet regularly to discuss suicide risk assessment, DSMP procedures, adequacy and assessment of training. Although all personnel will receive training, the SSI-C will only be administered only by trained clinicians (PIs/CoIs, Study Clinicians).

Primary Assessment Measure

2. A score > 6 on the SSI-C will prompt standardized suicide risk assessment and administration of The Suicide Checklist and Suicide Assessment Decision Tree (See Below).

a. If risk is elevated but not imminent, established behavioral methods will be used to effectively manage risk. The PI will closely monitor decision-making and assessment, and action taken will be clearly documented.

b. Imminent risk would usually result in participants being referred for immediate hospitalization and emergency mental health services. As the participants involved in this project will already be on the inpatient unit, the clinical staff will be notified and the PI/Co-Is will closely monitor decision-making and assessment, and action taken will be documented.

OVERVIEW OF SUICIDE RISK CATEGORIZATIONS

I. Previous Suicidal Behavior: Previous suicidal behavior represents the single most important factor in risk assessment, distinguishing 3 clinically distinct groups:

a. Suicide ideators
b. Single attempter
c. Multiple attempters

II. The Nature of Current Suicidal Symptoms: 2 Factors

a. Resolved Plans and Preparation. Symptoms (8): A sense of courage to make an attempt, A sense of competence to make an attempt, Availability of means for attempt,

Opportunity for attempt, Specificity of plan for attempt, Preparations for attempt, Duration of suicidal ideation, Intensity of suicidal ideation

b. Suicidal Desire and Ideation. Symptoms (9): Reasons for living, Wish to die,

Frequency of ideation, Wish not to live, Passive attempt, Desire for attempt, Expectancy of attempt, Lack of deterrents, Talk of death

III. Precipitant Stressors: Interpersonal losses (e.g., separations from loved ones), Interpersonal discord, Legal troubles, Physical or emotional abuse

IV. General Symptomatic Presentation, Including the Presence of Hopelessness: Axis I and II diagnostic comorbidity in MDD, Alcohol use, Hopelessness

V. Other Predispositions to Suicidal Behavior: Person-centered and background (internal static risk factors) examples: history of prior attempt (especially multiple attempts); past and current psychiatric history; chaotic family history, recent separation or divorce; history of physical or sexual abuse; family history of suicide and mental illness. Demographic variables examples: ethnicity (Caucasian or American Indian), age (elderly), gender (male), marital status (widowed or divorced). Behavioral factors: impulsivity or low impulse control

RISK CATEGORIZATIONS

Nonexistent or Minimal Suicide Risk

1. No identifiable suicidal symptoms, no past of suicide attempts or intentional self-harm, and no identifiable suicide risk factors present

Mild Suicide Risk

1. A multiple attempter with: no other risk factors
2. A nonmultiple attempter with:
    a. Suicidal "Desire and Ideation" of limited intensity and duration,
    b. No or only mild symptoms of the "resolved plans and preparation" factor
    c. No, or few other risk factors present

Moderate Suicide Risk

1. A multiple attempter with: any other notable finding
2. A nonmultiple attempter with moderate-severe symptoms of the "resolved plans and preparation factor"
3. A nonmultiple attempter with:
    a. No or mild symptoms of the "resolved plans and preparation" factor
    b. Moderate-to-severe symptoms of the suicidal desire and ideation factor
    c. At least 2 other risk factors present

Severe Suicide Risk

1. A multiple attempter with: any two or more other notable findings
2. A nonmultiple attempter with:
    a. Moderate/severe symptoms of "resolved plans and preparation" factor and
    b. At least 1 other risk factor present

Extreme or Imminent Suicide Risk

1. A multiple attempter with: severe symptoms of the "resolved plans and preparation"
2. A nonmultiple attempter with:
    a. Severe symptoms of "the resolved plans and preparation factor" and
    b. At least 2 or more other risk factors present

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