Neuroimaging of a Combined Transcranial Magnetic Stimulation and Brief Cognitive Behavioral Therapy to Reduce Veteran Suicide
IRB Protocol Version:
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INTRODUCTION

This study proposes to conduct a fully-powered randomized controlled trial (RCT) that will evaluate whether adding repetitive Transcranial Magnetic Stimulation (TMS) to Brief Cognitive Behavioral Therapy (BCBT) can reduce suicidality. We will also collect magnetic resonance imaging (MRI) and cognitive testing data from study participants in order to examine phenotypic biomarkers of suicidality and correlates of response to treatment. The proposal will target high-risk suicidal Veterans at the Providence VAMC, and deliver these interventions in the highest risk period after a suicidal crisis. We will randomly assign enrolled suicidal Veterans to either active TMS+BCBT or sham (placebo) TMS+BCBT. Outcomes will include assessments at: baseline (i.e., enrollment); weekly intervention therapy sessions; endpoint (last intervention therapy session); follow-up 1 (6-months from start of intervention); follow-up 2 (12-months from start of intervention); follow-up 3 (24-months from start of intervention). We will also collect MRI, cognitive, and health data from a limited number of non-suicidal Veteran control participants.

TABLE OF CONENTS

A. OBJECTIVES

Our study has two principle objectives: 1) to test the effect of combining repetitive TMS with BCBT on reducing Veterans' rates of suicide ideation and related behaviors and 2) to identify brain-based biomarkers of suicidality and responsiveness to suicide treatment.

A1. Significance

Suicide prevention is a priority of the VHA with national leadership setting the goal of getting Veteran suicide to zero. This study is designed to: decrease suicide rates in Veterans during periods of increased risk (i.e., post-hospital discharge, following a suicidal crisis); add to our knowledge of how to maximize treatment benefits for Veterans with suicidality; discover whether combining TMS to an empirically-based therapy for suicide increases effectiveness compared to BCBT monotherapy; and collect neurocognitive data that will facilitate future optimization of treatment delivery and prescription. Despite the promise of both treatment modalities – TMS and BCBT – to our knowledge no one has prospectively studied the combination of these two interventions. Furthermore, few studies conducted in Veterans have examined brain-based biomarkers of suicidality and/or response to interventions for suicide. Collectively, our team has expertise in suicide, TMS, and neuroimaging, and are well-qualified to evaluate the effectiveness and biological mechanisms of a combined TMS+BCBT treatment for suicide.

A2. Primary Hypotheses:

- Compared to sham TMS+BCBT, Veterans receiving active TMS+BCBT will demonstrate greater reductions in suicidal behaviors.
- Suicide symptom reductions after TMS+BCBT will be correlated with changes in brain function in executive control regions.

A3. Secondary Hypotheses:

Compared to sham TMS+BCBT, Veterans who receive active TMS+BCBT will have:

- Reduced suicide attempts and/or longer time to first attempt.
- Superior improvements in psychosocial functioning.
- Reduced suicidal ideation severity.
- Fewer psychiatric hospitalizations/crisis visits during the follow-up period.

A4. Moderator and Mediator Effects:

In addition to these specific hypotheses, we will conduct:

- Exploratory latent growth curve analyses to compare the trajectory of change for primary, secondary, and tertiary outcomes (i.e. linear ascending, descending, or quadratic between sham TMS+BCBT versus active TMS+BCBT.
- We will include moderator variables in these models (e.g. diagnosis, comorbidity, gender), which may identify specific patient groups who will benefit from the addition of active TMS+BCBT versus sham TMS+BCBT.
- We will investigate mediating variables to determine the mechanisms through which TMS produces its effects on clinical outcomes.

A5. Exploratory Brain-Behavior Hypotheses

- Brain and behavioral correlates of decision-making, impulsivity, and executive control at baseline will differ between Veterans with suicidality and non-suicidal Veteran controls.

- Improvement in suicide symptoms after treatment will be predicted by brain and behavioral correlates of decision-making and executive control at baseline.
- Improvements in suicidality will be associated with functional changes in decision- making circuits.
- Machine learning models predicting longitudinal outcomes that merge brain, cognitive, and electronic health record (EHR) data will outperform models based solely on EHR.

B. BACKGROUND

The tragedy of Veteran suicide cannot be overstated. Twenty Veterans die each day of suicide [1]. Suicide in female Veterans has increased substantially in the last 5 years [1]. Suicide attempt rates are also climbing. The Veterans' Health Suicide Prevention Application Network (SPAN) reported that over 900 suicide attempts per month occurred in 2014 – an unacceptable increase from 600 per month in prior reports [1]. The presence of a single episode of suicidal ideation or attempt places an individual at greatly increased future risk [2]. Research in civilian populations demonstrated that suicide attempters are 38 times more likely to die of suicide than those without history of attempts [3]. In the year following a suicide attempt, 0.8 – 2.6% of previous attempters died of suicide; mortality estimates 9 years post attempt are as high as 5-11%[4].
One estimate suggests that approximately 15% of all individuals with one or more suicide attempts will eventually die of suicide [5].

B1. Despite advances in psychiatric treatment, suicide rates have not decreased Psychiatric illness and substance use disorders are strongly associated with completed suicides and suicide risk [3]. Given the comorbidity between psychiatric disorders and suicidal behavior, one might expect a decline in suicidal behavior with recent advances in psychiatric care and the increased availability of medications and psychotherapy treatments. Yet, nationwide suicide completion rates have increased since the year 2000. Therefore, even though treatment of psychiatric disorders has made significant progress, suicide prevention efforts lag behind. New treatments, specifically those developed to prevent suicidal behavior and designed to work in concert with mental health treatment, are clearly needed. The Veterans Health Administration has been at the forefront of suicide research making it a top funding priority. Despite this investment, between 2000-2014, military suicide rates increased surpassing civilian rates for the first time in recorded military history [6].

B2. Time following discharge from hospital or a suicidal crisis is of high risk The period following discharge from a psychiatric hospitalization is a time of substantially increased risk for suicide [3]. The highest risk period is in the first month after hospital
discharge [2, 7]. Risk remains elevated up to one-year post-discharge estimated at a 30 to 60- fold increase [2, 7, 8]. Veterans who have recently experienced an increase in suicidal ideation or attempted suicide (i.e., a suicidal crisis) even in the

absence of hospitalization are also at increased risk for suicide. Thus, to be maximally effective, prevention efforts should focus on the year following hospitalization or suicidal crisis, a time of uniquely high risk for suicide.

B3. What we Know About Psychotherapy Treatments to Prevent Suicide

B3.1 Few trials have been conducted: Despite the public health significance of suicide, few controlled trials have evaluated interventions to reduce suicidal behavior. In their literature review for the Cochrane Library, Hawton et al. (2000) [9] identified 23 controlled trials of

suicidal behavior in adults. Though several additional studies have been published since this review [10-13], suicide treatment is clearly under-studied. Moreover, only a minority (< 20%) of these trials have been conducted in the United States, an important consideration impacting the generalization of findings given the differences in health care delivery systems between the US and other countries. Only one well-powered US-based published clinical trial evaluating an intervention to reduce suicidal behavior in adults has been conducted in the past 10 years [14]. Though a handful of trials are currently underway, the historical lack of US based clinical trials focusing on suicidal behavior is striking.

B3.2 Treatments are especially under-studied in Veterans: In 2015, a systematic review of suicide prevention in Veterans supported by the VA's Health Services Research and Development Service (HSR&D) concluded that there have been "insufficient studies of suicide prevention specifically in Veterans" [15]. This report reviewed all published suicide prevention intervention efficacy or effectiveness studies conducted between 2008 and 2015 that included Veterans, military personnel, or demographically comparable non-Veteran/military adults from the United States, the United Kingdom, Canada, New Zealand, and Australia. Only five randomized controlled trials met these inclusion criteria. In addition to these reviewed studies, results from five earlier RCTs also resulted in published findings [16], but these studies did not target Veterans and only one recruited directly from a military population [54]. In response to the increase in Veteran suicide, the VA and Department of Defense have increased funding and resources for suicide prevention work with Veterans and military personnel. Most funded studies however, are in their infancy and only a modest number of clinical trials have been implemented on a large scale compared to other lines of mental health intervention research.

B3.4 Results from available psychotherapy studies are mixed: Virtually all reviews of psychotherapy for suicide [12, 13, 15] have commented on the paucity of studies, small sample sizes, small effects and inconsistent results. Notably, few of these studies were conducted in Veteran/military samples and HSRD's review determined that many RCTs in Veteran/military samples were underpowered and yielded relatively small effect sizes [15]. The strongest findings come from individually based psychotherapy focused specifically on suicidal behavior, such as Dialectical Behavior Therapy [16] and Cognitive Therapy for Suicide Attempters [18].

Brief Cognitive Behavioral Therapy (BCBT) is an effective treatment for both depression and suicide [19] and works in military and VA settings [19]. In a recent study of military service members, suicide risk decreased 60% after participants received a course of BCBT [17] when compared to those who received treatment as usual. CBT is widely used by therapists throughout the VHA system and is considered standard of care for treatment of depression. Although Cognitive Behavioral Therapies decrease psychiatric symptoms and suicide, effect sizes vary significantly across studies ranging from (d= .18-.79) [20], with most RCTs finding effect sizes in the small to moderate range.

B3.5 Enhancing efficacy is crucial for the reduction of Veteran Suicide**:** In summary, suicide rates in Veterans continue to be unacceptably high and existing

treatments only reduce risk to a moderate degree. Furthermore, not all patients respond to standard psychotherapy treatments. Patients with severe symptoms tend to show smaller gains in symptom reduction after CBT than those with milder symptoms. These individuals are at significantly higher risk of dying by suicide. Consequently, finding ways to augment the effect existing treatments is critical.

B4. Transcranial Magnetic Stimulation: An ideal treatment to augment BCBT for suicide reduction

B4.1 What is Transcranial Magnetic Stimulation? Our novel approach to augment CBT for suicide is with repetitive transcranial magnetic stimulation (rTMS, hereafter TMS). This noninvasive treatment has been available since 2008 when it was cleared by the U.S. Food and Drug Administration (FDA) for pharmacoresistant major depressive disorder (MDD). TMS uses a pulsed magnetic field to induce neuronal depolarization in a targeted brain region, typically the left dorsolateral prefrontal cortex for MDD. TMS can effectively reduce symptoms of MDD as shown in the initial two large efficacy studies [21, 22]. Since that time, our group has been involved in evaluating the efficacy of TMS in naturalistic samples [23, 24] durability of effect [25], and efficacy in older individuals [26] and Veterans with depression and PTSD [26, 27] .

A distinct feature of TMS is that it is not associated with any of the systemic and costly side effects associated with standard antidepressant pharmacotherapy (e.g., weight gain, diabetes, sexual side effects). The most common side effects from TMS are treatment site discomfort, but it is associated with a rare (<1:300,000) risk of seizure [28]. It is an outpatient procedure and does not require anesthesia – Veterans receive their TMS and then later the same day attend work, school or other activities without limitation.

B4.2 TMS and Suicide: Despite the large number of studies demonstrating the efficacy of TMS to reduce symptoms of MDD [29], fewer studies have evaluated whether TMS can reduce suicidal thinking. One early study used a very small sample size (n=14) and experimental form of TMS and found no difference between active and sham stimulation on suicide risk [30]. Since that time, several larger studies have found promising results. The largest study to date (n=178) found that active TMS rapidly reduced suicidal thinking, compared to sham, [31]. This study used treatment settings identical to those used in our clinic and proposed here. Another study, which used an experimental form of TMS in Veterans, found initial rapid reductions in suicide only occurred in the patients that received active stimulation [32].

To evaluate whether TMS was associated with reductions in suicidality at the Providence VA, we reviewed the charts of the last 45 patients who received TMS at our Neuromodulation clinic. We found significant and clinically meaningful reductions in suicidal ideation and depressive symptoms (see **TMS Preliminary Data**). However, despite the promise of this prior data, no studies have combined TMS with evidence-based therapy for suicide to evaluate whether the combination could meaningfully reduce suicidality.

B4.3 Mechanisms of action of TMS and why TMS+BCBT makes sense to reduce suicidality: TMS is an ideal treatment to add to psychotherapy targeting suicide for several reasons. TMS typically targets the dorsolateral prefrontal cortex (DLPFC), a brain region involved in “executive function” or “cognitive control” i.e. the adaptive, goal-directed regulation of thought and action. Regulation of affective states, stress, and emotion responsiveness are key functions of the cognitive control system [33]. Notably, cognitive control and emotion responsiveness are both disrupted in suicidality [34]. As TMS has been shown to improve cognitive control in multiple studies of ill individuals [35], TMS may also

ameliorate impaired control in suicidality. These neurobiological mechanisms of TMS have important implications for TMS. DLPFC is highly involved in CBT [36]. One possible reason the modest effect sizes for BCBT is that it is being used by individuals who are not able to engage DLPFC. The effects of TMS + BCBT are potentially additive –TMS monotherapy reduces suicidality and pairing it with BCBT may allow Veterans to better utilize and implement lessons learned in BCBT as a result of improved cognitive control. Indeed, several studies indicate that stimulation augments cognitive control training [37, 38].

B5. Cognitive neuroscience approaches to suicide prevention.

B5.1 Neuroimaging and cognitive correlates of suicide: Suicide is a complex phenomenon and though we still have much to learn about the neurobiology of suicide, significant progress has been made over the last 30 years. Findings from previous MRI studies indicate that disruptions in the function and anatomy of the reward network are present in individuals with suicidality [39-41]. The reward network is comprised of ventral frontal cortex, striatum, and midbrain structures. Reward neurons compute the subjective pleasantness/unpleasantness of both current and expected sensations, objects, and events. Thus, these signals are an important component of the construction of emotion. As such, disruptions in the reward network may be central to emotional dysregulation in suicidality.

Beyond the reward network, cognitive control function has been implicated in how suicidal thoughts and behaviors are manifested. A recent influential model has proposed that suicide can be conceptualized as a maladaptive decision process, wherein the individual makes an instrumental choice to end their life [42]. Studies of decision-making have found a systematic relationship between the capacity to forego immediate rewards, and the lethality and planning of previous suicide attempts. Notably, those with history of highly planned and lethal attempts possess an exaggerated ability to delay gratification – a capacity normally associated with high cognitive control function [36,40]. Taken together, these theories and observations paradoxically suggest that in suicidal individuals, enhanced ability to control behavior may impart greater risk. Thus, neural correlates of cognitive control may prove to be a valuable biomarker of a high-risk subgroup, though more research in this area is needed.

B5.2 Objective bio-behavioral markers are needed to reduce Veteran suicide and optimize treatment:
Improving risk assessment tools is crucial for the early identification of at-risk Veterans and the prevention of Veteran suicide. Currently, assessments of risk are largely based upon self- reported suicidality. Though some patients accurately disclose suicidal thinking, others may be motivated to conceal or minimize their suicidality or may lack insight into their symptoms.

The findings discussed in section B5.1 indicate that including cognitive neuroscience approaches including neuroimaging and behavioral testing may be a promising means of understanding both the underlying pathology of suicide and the potential mechanisms of action for suicide interventions. Objective bio-behavioral markers sensitive to suicide risk severity or specific symptoms (planning or lethality) may be helpful for improving the identification of those at most imminent risk of making a suicide attempt. Biological markers may also improve clinical treatment by informing innovative, targeted treatments such as neuromodulation of implicated functional circuits in suicidal Veterans. Neuroimaging and cognitive data collected from Veterans taking part in this study will be used to identify potential objective markers.

B5.3 New approaches to risk modeling are needed to reduce Veteran suicide:
Even when risk information is accurate, traditional models based on a limited number of individual risk factors predict suicide with chance accuracy [43]. Since

assessments guide recommendations for proactive suicide interventions, clearly improving risk models is critical for prevention. Recent studies of electronic health record (EHR)-based machine learning models are promising, indicating that theses algorithms are better suited to the task of predicting multi-dimensional behaviors like suicide. Further attempts to refine and enrich these models with novel objective suicide correlates may further improve risk surveillance. Machine learning algorithms may also be clinically useful for predicting the likelihood that individual patients will respond to

treatments. Incorporating neurocognitive biomarkers identified from the proposed research into machine learning-based models of suicide is an avenue for improving risk assessment.

B6. Conclusion:

In summary, suicide rates in Veterans continue to be unacceptably high and existing treatments only reduce risk to a moderate degree but do not eliminate it. Furthermore, not all patients respond to standard psychotherapy treatments. Patients with severe depression and those with comorbid personality pathology tend to show smaller gains in symptom reduction after CBT than those with moderate-mild symptoms and no comorbid personality pathology.
Unfortunately, those with severe symptoms are at significantly higher risk of dying by suicide. Consequently, finding ways to augment the effect existing treatments is critical. TMS is an ideal treatment to add to brief cognitive behavioral therapy for suicide. It targets the same neurobiological mechanisms, it improves they types of executive functioning ability required for learning and retaining CBT skills, it is being rolled out at VAMCs across the country, and it may be a more acceptable treatment than pharmacotherapy. No studies have examined whether adding TMS to standard brief cognitive therapy increases the suicide prevention effect of BCBT therefore, we propose to examine whether combined TMS + BCBT enhances treatment outcomes. Importantly, by including MRI into the design of this study, we now have the methodological means to discover etiologically-relevant patterns brain function and treatment response.

C. PRELIMINARY

STUDIES C1. Pilot BCBT

Data:

Co-Investigator Ivan Miller, PhD has trained, supervised and conducted research utilizing Cognitive Behavioral Therapy for 30+ years, including multiple clinical trials involving cognitive therapy for severely depressed and suicidal inpatients [44-47]. MPI Jennifer Primack, PhD is a clinical psychologist, national expert in suicide prevention, and has worked closely with Dr.
Miller on several clinical trials. Dr. Bryan co-developed the BCBT protocol that will be used in this study [19] and may provide consultation on therapist training and assessment of treatment fidelity.

C2. Pilot TMS Data:

MPI Noah Philip, MD directs the Neuromodulation clinic at Providence VA Medical Center. He has published evaluations of TMS outcomes [24], multisite efficacy studies of TMS [23,25], and has been the PI of studies involving TMS (RR&D I21 RX002032 and NIH R21 DA042989). To evaluate the feasibility of TMS for suicide and inform power analyses and study design, we conducted a chart review of the last 45 Veterans who received TMS at our Neuromodulation clinic at the Providence VA Medical Center. We compared baseline and endpoint scores of MDD using two standardized rating scales, the Inventory of Depressive

Symptomatology, Self-Report (IDSSR) [48] and 9-item Patient Health Questionnaire (PHQ9) [49]. We then evaluated whether treatment was associated with reductions in depressive symptoms and whether TMS treatment was associated with reduction in the suicide items (i.e., items 18 and 9 on the IDSSR and PHQ9, respectively). Depressive symptoms were reduced significantly post-TMS ($p<.001$ for both the IDSSR and PHQ9). We also observed a significant reduction in suicide items on the IDSSR ($p = .025$) and PHQ9 ($p=.016$). Reductions in depressive and suicide symptoms were

highly correlated (all r>.55, all p <.005). This preliminary data shows that not only can TMS reduce symptoms of depression, but it can also reduce suicidality.

C3. Pilot Neuroimaging Data:
MPI Jennifer Barredo, PhD is a cognitive neuroscientist that has conducted basic and clinical neuroimaging research, including research in Veterans and in suicidality. In a recent publication co-authored with MPI Philip, she conducted a secondary analysis that used structural and functional neuroimaging to characterize features of brain organization associated with suicidality in Veterans and civilians with PTSD. This study found evidence of a systematic relationship between self-reported suicidality (item 18 on the IDSSR) and the structural and functional organization of executive control regions involved in inhibition and reappraisal.
Another manuscript under review summarizes a secondary analysis that identified brain circuits where functional changes are correlated with suicide symptom reductions (change in IDSSR item 18) after TMS. These preliminary studies demonstrate the feasibility of using neuroimaging to identify correlates of suicide symptom reductions after TMS.

D. <u>RESEARCH DESIGN & METHODS</u> D1. Participants
The study population will include Veterans 18-75 years old. They will be men or women from the greater Providence area receiving care at the VA who have been discharged from active duty, or who served in the National Guard or reserve units.

Two groups will be recruited. One group will consist of Veterans admitted to the PVAMC psychiatric inpatient unit or medical unit or identified in outpatient settings for suicide attempt or suicidal ideation with any degree of suicide plan, and/or intent to attempt suicide. This group of Veterans may be enrolled into either active or sham TMS+BCBT, if eligible. The second group will consist of DSM-V diagnosis-matched Veterans without current suicidality to act as controls. Controls will also be matched for age ± 5 years, and sex. The control Veterans, if eligible, may be enrolled in the neuroimaging and cognitive battery, and not be eligible to receive the TMS+BCBT intervention. The matching procedure is used to limit the influence disorder- specific characteristics, sex, and age-related brain/cognitive differences on group comparisons. If we are unable to meet annual recruitment goals, sex differences will be handled through statistical covariation and strata for age-matching will be broadened (±10 years).

D2. Participant Selection:
Participants will consist of Veteran inpatients or outpatients of the Providence VAMC with active suicide ideation or related behaviors, and non-suicidal Veteran controls. The inclusion and exclusion criteria are as follows:

<u>D2.1.Inclusion criteria:</u>

<u>Inclusion criteria for all participants:</u>

1) Participants must be Veterans aged 18-75 discharged from active duty, National Guard, or reserves units, receiving care at the VA. They must be able to comply with all study related procedures and visits and be

capable of independently reading and understanding study materials and providing informed consent.

Inclusion criteria for Veterans with suicidal thoughts and behaviors:

1) Admission to a hospital or identified in outpatient settings within 2 weeks of suicidal ideation with any methods, intent and/or plans, or within 2 weeks after an attempt as

indicated on hospital chart and confirmed by administration of the Columbia Suicidal Severity Rating Scale (C-SSRS).

Inclusion criteria for non-suicidal Veterans (controls)

1) No evidence of current suicidality in the medical record or endorsement of current suicidal thoughts and behaviors on the C-SSRS.
2) Matched to a participant with suicidal thoughts and/or behaviors on DSM-V diagnosis, age ± 5 years, and sex.

Exclusion criteria:

Exclusion criteria for all participants:

1) Primary psychotic disorder (e.g. schizophrenia, schizoaffective disorder)

2) Cognitive impairment (as indicated by neuropsychological evaluationsand/or diagnoses related to cognitive impairment [e.g., dementia] in the chart)
3) Pregnancy/lactation, planning to become pregnant during the study, childbearing potential and does not agree to consistent use of a measure of birth control during the scanning and TMS portions of the study. Confirmation of non-pregnancy among hospitalized patients will be obtained from the medical record review as pregnancy tests are required for psychiatric hospitalization. Pregnancy tests will be administered prior to MRI scanning and/or TMS for control participants or suicidal participants identified outpatient.
4) Lifetime history of moderate-to-severe traumatic brain injury.
5) Current unstable medical condition.
6) Current (or past, if appropriate) significant neurological disorder.
7) Lifetime history of: seizures, CNS tumors, stroke, cerebral aneurysm.
8) Active moderate-to-severe substance use disorder (within last month, excluding nicotine/caffeine dependencies).

Exclusion criteria specific to TMS+BCBT:

1) For safety, participants must meet established screening criteria following MRI safety. MRI involves magnetic fields at similar intensity to those emitted from the TMS stimulation coil. Unless devices are MRI-safe patients may not have:
    a. Cardiac pacemaker, implanted device (deep brain stimulation) or metal in the brain, cervical spinal cord, or upper thoracic spinal cord
2) Other exclusions include conditions that could be worsened by TMS, such:
    b. Bipolar I disorder or an increased risk of seizures in the case of severe and uncontrolled substance use disorder
3) Patients who have previously received Theta Burst Stimulation cannot be enrolled in this study
    a) The risk of the patient recognizing the difference between active versus the sham would jeopardize the double-blinding framework proposed in this protocol as well as the credibility of reported data.

Exclusion criteria specific to Neuroimaging:

1) MRI contraindications (e.g., cardiac pacemaker, non-MRI safe implants, shrapnel, permanent makeup).

D2.2 Feasibility of enrolling targets: The enrollment, recruitment, and inclusion/exclusion criteria used in this study were modeled after procedures used by Dr. Jennifer Primack in her PVAMC IRB-approved study "Veterans Coping Long Term with Active Suicide." Dr. Primack's staff screened 168 potential patients from the PVAMC inpatient unit ultimately enrolling 100 participants in 3.5 years of active enrollment. In her study, thirty-five (21%) of screened individuals were excluded for with borderline personality disorder which is not exclusionary for this study. We expect that ~20% of potential participants will have an MRI contraindication based on exclusion rates from PVAMC IRB-approved studies (PI: Noah S. Philip, M.D.). Enrollment targets are feasible, especially given the longer 5-year timeline of this study.

D3. Pre-screening, Recruitment, & Informed Consent

D3.1 Identification and Pre-Screening of Potential Participants: Pre-screening allows for the identification of a rare, low base rate study population. Pre-screening will also allow us to identify potential diagnosis, sex, and age matched Veteran controls while minimizing the number of screens reducing burden for potential participants. We will administer MRI and TMS safety questions verbally to interested potential participants during either in-person or telephone pre-screening to limit burden of completing informed consent for individuals that cannot be scanned or stimulated safely (e.g. shrapnel not reported in medical record, history of metal-work without proper protective gear, permanent makeup). Please see questionnaires for additional information.

D3.1.1 Pre-Screening of Potential Participants with STBs.
A HIPAA waiver will be obtained for screening purposes. Veterans will be recruited from the psychiatric inpatient units or outpatient care at the Providence VAMC through three primary strategies:

1) **Chart reviews**: Research staff will screen charts daily for patients newly admitted to the inpatient unit for suicidality. Identified charts will be screened for MRI and/or TMS contraindications (e.g. pacemakers) and other medical exclusionary criteria.
2) **Suicide Prevention Coordinator (SPC) referrals**: Research study staff will also check -in with the local SPC or SPC staff bi-weekly to identify potential study participants.
3) **Clinician referrals**: A member of the research staff will visit the inpatient unit weekly to consult with staff about potential study participants. Research staff will also introduce the study to mental health professionals at psychiatric outpatient clinics at the Providence VAMC.

For prospective patients in inpatient settings: If clinical staff deem that participation is appropriate for the Veteran under consideration, study staff or treatment staff familiar with the study will provide a description of the study and study aims *(see attached Study Overview and Combined Study Overview*). They will inform the patient that research staff will visit over the

next few days to provide further detail about the study and discuss if interested and eligible to participate.

For prospective patients in outpatient settings: We will give providers and clinicians IRB-approved study brochures (*Study Overview and Combined Study Overview*) to distribute to potential participants. If a potential participant expresses interest in the study, clinicians will send study staff an encrypted email with participant's last name and last four SSN. We will then send the Veteran an official recruitment letter including information about when we plan to contact the Veteran. If the Veteran prefers not to wait for an official letter, they will be notified that they can to call study staff using the contact information on the recruitment brochure. IRB-approved study brochures and flyers (*Combined Study Flyer*) will be posted in PVHCS outpatient waiting areas.
Interested participants may contact our study team using the contact information on the brochure and flyer at their own discretion.

Any pre-screening assessments collected from any Veteran who does not meet pre- screening eligibility criteria or who is uninterested in participating in the study will be destroyed in accordance with VA policy. Any assessments collected for these individuals will be destroyed in appropriate locked shredding bins available throughout the hospital and research building as soon as possible upon completion of the meeting. If a potential participant does not participate in the study, they will continue with their usual mental health care plans. If a potential participant declines to participate when approached or contacted by study staff, staff will ask for permission to take a one-question verbal survey as to why they are declining participation. This response will be recorded on a form by study staff. This response will not be linked to the patient in any way. This data will only be used by Investigators as a systematic way of understanding our recruitment population.

Veterans deemed initially eligible at completion of pre-screen, endorsing suicidality in the prior 2 weeks(as indexed by the C-SSRS) and meeting MRI and/or TMS safety
requirements, will be asked to complete an informed consent form followed by baseline assessments as part of the study and to further confirm continued eligibility. This process can take 2 to 3 hours to complete.

D3.1.2 Pre-Screening of Potential Participants without STBs (controls)
1)**Chart reviews**: Research staff will use CPRS to identify potential matched Veteran controls. Matching limits the influence disorder-specific characteristics, sex, and age- related brain/cognitive differences on comparisons between Veterans with and without STBs. If we are unable to meet recruitment goals, age-matching strata will be broadened (±10 years). We will review charts for MRI contraindications (e.g. pacemakers) and other medical exclusions such as primary psychotic disorder, history of moderate-to-severe TBI and by the age, sex, and DSM-V diagnosis of Veterans with STBs enrolled in the study. Study staff will send potentially eligible Veterans an official letter explaining the study and indicating that a

specific research staff member will contact the patient on a specific day about the study. Staff will call the patient on the designated date.

2) **Clinician referrals**: Study personnel may contact providers and staff in the Primary Care Behavioral Health, Psychiatric Neuromodulation, Polytrauma, Trauma Recovery Service clinics for referrals for potential control participants. Clinicians will ask if potential participants are interested in learning more about the study and if a patient expresses interest, the clinician will inform study staff. Study staff will then send the potentially eligible Veterans an official letter (see above). Or, if the Veteran prefers, the clinician will call study staff directly. If available, a member of the research staff will meet the potential participant at the clinician's office and will walk them to PVAMC bldg. 32 where they will talk with the patient about the study and answer any questions.

D3.2 Pre-screening Log: The information reviewed during the initial medical record pre-screen process (e.g. Patient name, date of birth, telephone number, provider, and contact history) will be recorded in a recruitment log once the patient has been identified as potentially eligible. This information allows us to track recruitment efforts and contact potential eligible participants. Additionally, this information is necessary for tracking recruitment, contacting patients, and conducting follow-up procedures. The recruitment log will be stored in a restricted folder on the secure Providence VA research server, which will be accessible only by study staff (*see F. Privacy, Information, and Confidentiality Security for full details*).

Due to the confined nature of our recruitment to one inpatient unit and outpatient referrals at the Providence VAMC, it will be necessary to keep this log until the end of the study. This log will be updated if any patient becomes ineligible or declines participation at the in-person pre- screening. It will also be updated to track and confirm we are not contacting/burdening the same patients over the course of the study who may have been ineligible or uninterested previously. It is necessary to keep recruitment log entries for ineligible or uninterested patients until the end of the study for this purpose.

At the end of the study, all recruitment log data from participants who were pre-screened but not enrolled will be permanently deleted/destroyed. At all times, the recruitment log will be kept separately from all other data from this study (*see F. Privacy, Information, and Confidentiality Security for full details*).

D3.3 Enrollment and Informed Consent of Potential Participants: Group specific procedures are detailed below. Written informed consent will be obtained from all participants. Participants that consent to participate but are excluded during later assessments and interviews will receive
$25 compensation for their time.

D3.3.1 Potential Participants with STBs
Informed consent and enrollment screening of Veterans with STBs will occur in-person while the participant is on the inpatient unit or during a

research appointment at PVAMC Building 32 for patients identified through outpatient settings. Research staff will coordinate with inpatient and referring outpatient staff to ensure that a) the patient is able to understand the study and research requirements and b) the informed consent, screenings, assessments, and intervention sessions are minimally disruptive. Patients that potentially meet study criteria after pre-screening will be provided with a description of the study and study aims, and asked if they would like to participate in a screening procedure to determine eligibility. If they are interested, they will complete informed consent prior to enrollment screening.

D3.3.2 Potential Participants without STBs (controls)
All informed consent and enrollment screening will occur in-person in a private consult room in PVAMC bldg. 32. During this interview, potentially eligible participants will be provided with a description of the study and study aims and asked if they would like to participate in a screening procedure to determine eligibility. If they decide that they are interested in participating, they will complete informed consent prior to any assessment or study participation.

D3.3.3 Contacting Participants:
Study staff may contact participants (potential or consented) via telephone or USPS mail. Materials sent via USPS may include COVID-19 Participant Packet, approved recruitment materials, therapy treatment materials (i.e., handouts or worksheets, consistent with good clinical practice), or questionnaires discussed during follow-up telephone visits.

In the instances in which a participant does not have a permanent domicile and is unable to receive mail, or an in-person appointment needs to become a telephone visit due to inclement weather or pandemic concerns, study staff may send pertinent materials via encrypted electronic mail at the request of the participant. These emails will be sent using Azure RMS encryption. Participant email addresses will be obtained and confirmed during the consent process and associated risks will be explained. If the instance does occur where mailing will not suffice, study staff will again receive verbal confirmation from the participant before sending study materials via encrypted email.

The subject lines of the encrypted email will read “Requested Information Attached.” Encrypted emails sent to participants will not contain any PHI/PII and will contain the following text in the body:

“Please find attached the requested information. Email is not secure. Please do not reply back to this message with any personal information or health information. Please call x#### with any questions.”

In the event a participant replies to an encrypted email sent by study staff, study staff will NOT reply to the participant's email, but will instead call the participant to answer any questions.

D4. Study Procedures

Participants will be assessed at baseline, fMRI visits (if eligible), during weekly therapy intervention sessions (if eligible), follow-up 1, follow-up 2, and follow-up 3.

Study Sessions	Baseline Visit	MRI 1 *As soon as scheduling allows after baseline visit*	Intervention Visits *Begin as soon as scheduling allows after baseline visit*			MRI 2 *As soon as scheduling allows intervention completion*	Follow-Up Visits (3 total) *6-, 12-, and 24-months from first treatment visit*
Session Duration	2-3 hours	2 hours	TMS 15 mins. (up to 5 times/week for 15-36 visits)	BCBT 1 hour (12 weekly sessions)	Endpoint 2 hours (at the last BCBT session)	2 hours	2 hours
Compensation	$75 ($25 screening, $50 completion)	$75	N/A		$50	$75	$50, each follow-up visit

D4.1 Baseline Visit

Research staff will complete baseline assessment measures with eligible participants once screened, consented and confirmed eligible. The baseline assessments will be completed on the same day as the initial screening, consent and eligibility determination. If needed, baseline activities can be extended into a second day to lessen patient burden. Baseline visit activities for Veterans hospitalized for suicidality will take place in a private conference room within inpatient units (psychiatric and medical units being used to treat psychiatric patients) at the PVAMC under the supervision of the PI or trained study staff, or in a private room at Building 32 for patients identified through outpatient care. In the rare case that hospitalized patients cannot be screened on the unit (e.g., discharging too quickly to screen), baseline visit activities can occur in PVAMC building 32 under the supervision of the PI or trained study staff following discharge from the hospital. Activities for control participants will take place in a private consult room in PVAMC bldg. 32. Participants not on the in-patient unit will complete urine/breathalyzer screens and will be removed from the study for a failed drug screen.

Participants will be compensated $75 for completion of the Baseline visit ($25 for completion of screening procedures, $50 for remainder of visit).

D4.1.1 Assessments

Participants will be assessed in-person at baseline. In addition to demographic variables, we will conduct assessments in seven areas: a) psychiatric diagnosis, b) suicidality, c) trauma, d) depression and anxiety, e) sleep, f) and impulsivity. Measures are listed in Table 2. A Description of measures and their psychometric properties is limited to the references.

D4.1.1a Assessment Personnel Training

All assessments will be conducted by trained interviewers and will be supervised by study Co- PIs. Our training procedures consist of: a) review of relevant written materials, b) didactic instruction from senior staff and experienced interviewers, c) practice interviews with review, feedback and reliability ratings from senior staff and experienced interviewers and d) continued practice, training and feedback until high agreement with established consensus ratings are met (e.g. three consecutive C-SSRS ratings are within 2 points of our consensus ratings). Additionally, all interviewers will be certified on the C-SSRS using established training procedures. Following initial training, all interviewers and senior staff will meet to review any questions/issues as needed.

Assessment		Collected At:
Demographics, Safety, and History		
	Demographics	BL
	TMS Safety Form	BL
	MRI Safety Form	BL
	Treatment History	BL
	Treatment Utilization (chart review)	BL, EP, F/U
	Treatment History Interview (THI)	EP, F/U
	TBS Blinding Assessment	EP
Diagnosis and Cognitive Impairment		
	Montreal Cognitive Assessment (MoCA)	BL**
	Structured Clinical Interview for DSM-V (SCID-V)	BL
	McLean Screen for Borderline Personality Disorder (MSBPD)	BL
	Alcohol Use Disorders Identification Test (AUDIT)	BL, EP, F/U
	Drug Use Disorders Identification Test (DUDIT)	BL, EP, F/U
Suicidal Thoughts and Behaviors		
	Columbia Suicidal Severity Rating Scale (C-SSRS), including Military- Specific Risk Assessment Questions	BL, EP, F/U
	PhenX Beck Scale for Suicide Ideation (SSI)	BL, , I^, F/U*
	PhenX Self-Injurious Thoughts and Behaviors Interview (SITBI, Items 51-72)	BL**, EP, F/U
	Longitudinal Interval Follow-Up Evaluation (L.I.F.E.) - sections: suicidal ideation and behavior	EP, F/U
	Beck Hopelessness Scale (BHS)	BL, EP, F/U
	Brief Symptom Inventory (BSI)	BL**, EP, F/U
Trauma		
	PTSD Checklist (PCL-5)	BL, I, EP, F/U
	Childhood Trauma Questionnaire (CTQ)	BL**
	Deployment Risk and Resilience Inventory (DRRI, Sexual Harassment, Combat Subscales)	BL**
Depression and Anxiety		
	Inventory of Depressive Symptomatology (IDS-SR)	BL, I, EP, F/U
	Depression, Anxiety, and Stress Scale (DASS)	BL**, F/U
	World Health Organization Disability Assessment Scale 2.0 (WHODAS 2.0)	BL**, EP, F/U
Sleep		
	Pittsburgh Sleep Quality Index (PQSI)	BL**, F/U
Impulsivity		
	PhenX UPPS Impulsive Behavior Scale	BL**
	The Barratt Impulsiveness Scale (BIS-11)	BL**

Table 2. Assessment battery.
BL = Baseline visit
BL** = If assessments are not completed at baseline visit, they may be completed at next research appointment (i.e., first MRI appointment)
I = Intervention – weekly (every 5 session) rating scales are assessed following standard PVAMC clinical neuromodulation treatment protocols
I^ = Assessment is given during the 12 weekly BCBT therapy visit
EP = 12th intervention therapy visit, 12 weeks (3 months) from start of intervention
F/U = 6-, 12-, and 24- month follow-up visits. Veterans will attend the follow-up visits per study involvement as described in *Section D4.1 Study Visits.*
F/U* = Measure is not administered in the absence of history of STBs

D4.2 MRI Visits and Cognitive Battery

All MRI visit activities (pre-intervention/post-intervention and for control participants) will involve the same procedures. Specifically, all will include self-reports, a brief battery of PhenX and NIH Toolbox cognitive test delivered via iPad, and an MRI scan. All visits will take place in a private consult room in PVAMC building 32 and the PVAMC MRI Suite.

MRI Visit 1 activities will occur as soon as scheduling allows after baseline visit, prior to the start of TMS+BCBT intervention, if applicable, and MRI Visit 2 will occur post-intervention, if applicable, as soon as scheduling allows following the final intervention appointment. Control participants will have the MRI visit as soon as scheduling allows following the baseline visit.

Cognitive testing data is collected with a laptop during some MRI scans. Images will be acquired on a Siemens (Erlangen, Germany) PRISMA 3T scanner and 64-channel head coil at the PVAMC MRI facility. All equipment used in the scanning room are MRI compatible. Participants will receive $75 for completion of the MRI visit. Compensation will be prorated for participants who do not complete the MRI scan if an attempt to complete the MRI scan is made.

D4.3.1 Urine and breathalyzer screens: All participants will complete urine/breathalyzer screens prior to the neuroimaging and cognitive battery. Participants will only undergo the urine/breathalyzer screens if they are participating in the neuroimaging portion of the study, prior to each neuroimaging and cognitive battery visit. The urine and drug screen will be evaluating active use of alcohol and the following substances prior to a participant entering an MRI scanner: amphetamines, barbiturates, buprenorphine, cocaine, marijuana (THC), methamphetamine, MDMA, opiates, oxycodone, phencyclidine, and propoxyphene. Since THC can be detected on drug tests for up to 30 days after use, we will confirm with participants that they are not actively under the influence of THC before proceeding with other study procedures. During consent and throughout the study, research staff will clearly explain the purpose of the breathalyzer and urine drug screens, informing participants that that they will be removed from the neuroimaging portion of the study for failure of a drug screen.

If a participant is involved in both the neuroimaging and treatment aspects of the study and fails the drug screen, they will still be eligible to participate in the treatment arm of the study. Prior to each administration of TMS, participants will answer questions regarding recent (i.e., current intoxication) drug and alcohol use per existing VA TMS protocols to ensure safety during the administration.

Study staff will use protective clothing (e.g. gloves) during collection of urine and breath samples for alcohol and drug screens prior to cognitive testing. Staff are required to wash their hands after disposal of urine and breathalyzer guards.

D4.3.1a Breathalyzer

1) A new mouthpiece will be used for each participant. Study staff will assist the participant with the breathalyzer placing it in the participant's mouth and holding it during testing.
2) The mouth piece will be disposed of into regular trash after the test.

D4.3.1b Urine drug screens

1) The participant will be instructed to go to the bathroom and give a sample.
2) Participant will be instructed to make sure the sample lid is closed and to place it on the designated tray for the research staff to review.
3) Participant is to wash his/her hands after using the bathroom for sample collection.
4) Study staff will examine the cup for positive readings on any indicator strip after the allotted time to results has passed per manufacturer instructions.
5) Study staff will empty the cup into the toilet and will flush the urine down the toilet
6) Empty cups will be disposed of in receptacles appropriate for urine per by VA regulations
i.e. red bags.
7) Urine kit tray will be de-sanitized with appropriate wipes.

D4.3.2 Decision-making tasks: These tasks will be used to measure differences in decision- making behavior between non-suicidal Veterans and Veterans with STBs.

D4.3.2a PhenX Toolbox Monetary-Choice Questionnaire[50]

A 27-trial questionnaire measuring the participant's willingness to delay immediate rewards in favor of a later, bigger reward. Two reward options will be presented to the participant on every trial of this verbally administered task.

D4.3.2b PhenX Toolbox The Iowa Gambling Test™ [51]

This measure of risk-tolerance will be administered via iPad. Participants are given a "loan" at the start of the task which they use to place "gambles" on cards selected from four different decks, one card per trial. Cards either add or subtract from virtual winnings. The goal is to maximize profit over the length of the task. Two of these decks yield small rewards/punishments and a modest small profit over time, the other decks yield large rewards/punishments and large losses over trials. Dependent measures are total winnings, and number of high/low risk selections.

D4.3.3 Cognitive Control tasks: These are used to characterize differences in cognitive control function between Veterans with and without STBs, and to examine the influence of cognitive control function, on decision-making and STBs.

D4.3.3a *NIH Toolbox Dimensional Change Card Sort Task* [52]

A measure of cognitive flexibility. On each trial, picture cards that vary along two dimensions (e.g., shape and color) are presented via iPad with the NIH Toolbox. Participants sort cards according to one dimension, but criteria change over the course of the experiment.

D4.3.3b *NIH Toolbox Flanker Task* [53]

The Flanker tests inhibitory cognitive control and attention. On each trial, the participant reports the direction of an arrow stimulus presented in the center of an iPad screen via key press. The central arrow is flanked by additional

arrows on either side that either point in the same (congruently) or opposite (incongruent) direction from the central arrow.
Suppressing attention to the potentially interfering peripheral arrows requires cognitive control.

D4.3.4 MRI Procedures:

D4.3.4a Patient Preparation for MRI. PI or trained study staff will discuss MRI Visit procedures, including safety measures, in detail with the participant prior to MRI Visit. Participants will complete urine and breathalyzer screens following the protocol described above. Participants will be asked to change into hospital gowns/scrubs prior to scanning. Subjects will be screened for the presence of a metal implants or accidental lodging of metal fragments three times: 1) by the PI or study staff conducting the enrollment screening, 2) by the PI or study staff at the MRI facility outside of the scanner room during Visit 2, and 3) by the MRI technician just prior to entering the scanner room.

Sequence	Localizer	MEMPRAGE	Resting State (MB=2)	Reward Task (MB=2)	SSRT Task (MB=2)	DSI (MB=2)
Slice (mm)	10	1	2.4	2	2	2
TE (ms)	5	1.69	32.6	28	28	71.6
TR (ms)	20	2530	1000	1000	1000	3600
FOV (mm)	2802	2562	2112	1922	1922	2082
Orientation	Sagittal		Axial			

Table 3. MRI acquisition sequences. Abbreviations as follows: TE = time to echo; TR = repetition time; FOV = field of view; MB = multiband; MEMPRAGE = multi-echo MPRAGE; SSRT = Stop-signal reaction time; DSI = diffusion spectrum images.

D4.3.4b MRI Acquisition Procedures. Sequences are all FDA-approved Siemens product sequences (detailed in Table 3). Scans include a low-resolution localizer (to plot slices), a high-resolution multi-echo MPRAGE structural scan for morphometry, a field-mapping scan used to identify inhomogeneities in the magnetic field, resting and task functional MRI scans which measure the blood oxygen level-dependent signal, and a high-resolution diffusion scan to visualize white matter anatomy. Multi-band imaging is used to enable rapid, high-resolution scanning. Scan order is detailed in Table 4.

D4.3.4c Patient monitoring during MRI scans. MRI operators and study staff will monitor the participants using 2-way voice intercom and infrared camera. Participants will be trained by study staff to use a hand-held squeeze bulb to signal that they need to communicate with scanner operators and study staff prior to scanning. Study staff will ask participants to confirm that they are comfortable and able to continue with the session periodically throughout the scanning session.

D4.3.4d Procedure for incidental findings. This protocol is not optimized or intended to diagnose neurological conditions. However, if a MRI image appears abnormal, study staff or MRI operators will inform the PI of the abnormality, but are not permitted to communicate the suspected incidental finding to the participant. The PI will consult with a radiologist at

the Providence VA Medical Center who will examine the images to determine if an abnormality is present and requires medical attention.

Run	Duration (sec)	Sequence	Task	Volumes (TRs)
--	9.2	Localizer	N/A	N/A
1	362	MEMPRAGE	N/A	N/A
2	69	Field Map	N/A	N/A
3	360	Resting-state fMRI	Passive fixation	150
4	360	Resting-state fMRI	Passive fixation	150
5	480	Task fMRI	Reward Task	480
6	480	Task fMRI	Reward Task	480
7	312	Task fMRI	SSRT Task	340
8	312	Task fMRI	SSRT Task	340
9	479	3-shell DSI	Video Option	N/A

Table 4. MRI acquisition order. Abbreviations as follows: TE = time to echo; TR = repetition time; FOV
= field of view; MB = multiband; MEMPRAGE = multi-echo MPRAGE; SSRT = Stop-signal reaction time; DSI = diffusion spectrum images.

D4.3.4e fMRI tasks. Custom-coded Matlab-based experimental control scripts are installed on a research-owned Apple laptop computer that is synced to the MRI scanner. These programs deliver visual task stimuli to a high-resolution MRI-safe display positioned at the back of the scanner bore. Behavioral responses collected via a MRI-safe button box are also relayed to the laptop during scanning.

I. Resting-state fMRI

Functional MRI data are collected while participants are quietly resting in the scanner. Participants will be instructed to visually fixate on a white crosshair presented in the center of a black background while remaining as still as possible during the scan.

II. Reward expectancy task

This task identifies brain areas involved in processing rewards and expected values. [54,55]. The task is divided into two, 48 trial, 7-minute scanner runs (Figure 2). On each trial, participants virtually "bet" via button press whether the number on the next card displayed (range=1-9) will be higher or lower than 5 (guess (?) phase). Next, an expectancy card is shown communicating the likelihood that the bet will result in a win, a loss, no change, or win/loss equally likely (cue phase). The number is then shown (# phase), followed by the win/loss amount (feedback phase). Expectancy cues are accurate on 50% of trials (except for neutral trials) producing neural "prediction errors" on misleading cue trials. Trials are separated by a 0.5–1.5s jittered inter-trial interval. Trial order is randomized with 12 trials per category (win, loss, neutral, ambiguous).

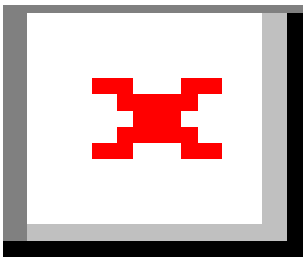

Fig. 2 The reward expectancy card guessing task[54] On each trial, participants guess (?) whether the number on a later card (#) is higher or lower than 5. An intervening cue card (Cue) sets an outcome expectancy. Feedback ($) after the card reveal corresponds to wins, losses, or a push. The difference between the actual outcome – win, loss, or push ("$") – and the expected value is the prediction error.

III. Stop-signal reaction time task (SSRT)

The SSRT measures inhibitory cognitive control [57,58] The task is divided into two, 128 trial scanner runs. On each trial, participants indicate whether a visually-presented 'go' arrow stimulus points to the left or right (50/50% probability) using a MRI-safe button box. During 25% of trials (random assignment), a stop-signal (up arrow) indicating that responses are to be withheld is delivered at a delay after the go arrow. On stop trials, the delay between the go cue and the stop signal is the 'stop-signal delay' (SSD). The SSD is varied based on performance[58]. Null events ranging from 0.5 and 4 s (mean, 1 s) will be interspersed between trials.

D4.4 Intervention [(active or sham) TMS +BCBT]

If eligible and willing to participate in the intervention, participants will be scheduled for the start of TMS+BCBT as soon as scheduling allows following the baseline visit and following their first MRI visit (if applicable). However, for

participants who are scheduled to start the intervention phase more than 2 weeks after the baseline visit, the C-SSRS, IDSSR, and PCL-5 will be readministered within 1 week prior to start of intervention.

The intervention period will consist of 15 - 36 visits occurring up to 5 days per week on business days (Monday – Friday) of TMS (either active or sham as assigned). All participants will receive BCBT. BCBT will be provided one time per week following a TMS session. TMS sessions will be modeled after those delivered in the PVAMC Psychiatric Neuromodulation Clinic, using

implemented safety and administration procedures. Individual stimulation sessions can last up to 15 minutes. BCBT sessions will last approximately 60 minutes. Days with TMS+BCBT sessions will require the participant to be available for approximately 1 hour and 15 minutes. The intervention period will last for 3 months (12 weeks) with TMS ending prior to the end of the 12 weeks.

D4.4.1 TMS Procedures: Participants will receive a form of TMS, using theta burst stimulation (TBS), a novel form of TMS with the benefit of much shorter administration time (i.e., standard TMS = 45 minutes per session, versus TBS = 3-10 minutes). The PVAMC Psychiatric Neuromodulation clinic is currently switching over TBS for standard clinical care following the publication of a large (N>400) non-inferiority study showing this form of TMS is equivalent to standard TMS. TMS in this study will start as soon as scheduling allows postbaseline visit.

All TMS will utilize a MagStim Super Rapid 2+1 system; two systems are available at the Providence VA. Prior to each TMS session, an un-blinded study member will assure the setup of either active or sham coil according to the participants' randomization code.

TMS procedures will start with a motor threshold determination, defined as the amount of energy required to induce movement in the contralateral hand in at least 50% of stimulations. Because using the treatment coil for motor threshold determination could lead to un-blinding, an unblinded 70mm coil will be used for motor threshold determination. Clinic staff will then position the TMS coil over the dorsolateral prefrontal cortex using the Beam/F3 method [59,60]. TMS sessions will occur business weekdays (typically 5 per week) up to 30 treatments, followed by six taper treatments over the subsequent three weeks [61,62]. We will use standard left sided, high frequency stimulation parameters following those utilized in our clinic to maximize safety and efficacy [25] in Veterans [22].

TBS parameters include intermittent TBS of 600-1800 pulses, delivered at up to 120% of motor threshold (based on [63]; and Philip et al., American Journal of Psychiatry under review). We will follow all standard TMS operating procedures, including those regarding rating scales, safety and administration.

Following our standard operating procedures, during TMS sessions Veterans will sit quietly wearing hearing protection and will not interact with study staff unless there are problems related to device positioning, etc. Motor threshold determination may be repeated if clinically warranted. The minimum number of TMS sessions in the acute series will be 15. The treatment series may conclude before #36 if a patient demonstrates two consecutive weeks of remission. Remission and number of sessions required will be determined by checking rating scales following standard clinical procedures (e.g., using the inventory of depressive symptomatology (IDS-SR <15)).

Safety will be assessed at every TMS session by recording spontaneously reported

adverse events. Participants will be queried daily about potential side effects associated with TMS such as headache and dizziness as well as any changes in medications, usage of drugs or alcohol, and mood. We will use a standardized self-report questionnaire (the TMS Daily Screener) to ask these questions. The TMS Daily Screener is administered by TMS staff on a dry- erase sheet without any identifiable information or participant ID. Responses on this screener are used to determine participant safety for daily TMS procedures, are not recorded/saved as

part of study data collection, and are erased at the end of the TMS session. If any reported
changes indicate that TMS administration may be unsafe, the session may be rescheduled. If reported changes are significant e.g., previously unreported consumption of illicit drugs that contraindicate TMS administration (i.e., render administration unsafe), the participant may be removed from the treatment part of the study. Participants discontinued from treatment may still be eligible for follow-ups associated with the MRI component of the study and will be asked if they wish to continue with that portion of the study. Following standard TMS operating procedures, a TMS technician will monitor participants for treatment-emergent safety issues such as seizures. Side effects will be coded using the current version of the Medical Dictionary for Regulatory Activities, following procedures used in prior TMS studies [64,65]. As described above, participants will be required to wear hearing protection during TMS. Reflecting the at- risk nature of the Veteran participants, a licensed physician with experience with neuromodulation and suicidality will always be available during study procedures.

D4.4.1a Considerations regarding pregnancy

TMS has been safely used on pregnant women, (e.g., [6]), but it is not FDA cleared for use in this population. We will utilize standard practices for investigational device and investigational TMS research (e.g., [25]). As noted above, pregnancy/lactation, planning to become pregnant during the study, or those who do not agree to consistently use a measure birth control during the study are excluded. Pregnancy tests are administered as part of standard clinical procedures during hospitalization. We will administer pregnancy tests to women identified in outpatient settings to verify safety for TMS/MRI. Participants will be asked to inform study personnel if they become pregnant; participants may also be asked to receive a urine pregnancy test if situations emerge where there is a possibility of pregnancy. Prior to the administration of each TMS session participants will be asked about any changes in medications, this includes birth control use. Participants will re-affirm continued use of their designated choice of birth control. Because pregnancy is an exclusion criterion, if they become pregnant during the study they will be removed from participation and managed following best clinical practices.

D4.4.1b TMS Assignments [active VS sham]:

We will use the urn randomization strategy and ensure balance among treatment groups [67,68]. We have successfully used urn randomization in previous treatment studies [44, 69] and developed a computer program that conducts the randomization. Urn randomization is a biased coin randomization technique, which randomly assigns Veterans of a given subgroup to treatment conditions (i.e., active TMS+BCBT or sham TMS+BCBT) while systematically biasing randomization in favor of balance among the treatment conditions on select variables. This program enables ongoing monitoring of the effectiveness of our stratification and randomization procedures. Since the number of variables which can be successfully balanced is limited, for the current study we will include the following variables in our randomization: a) current

admission due to suicide attempt vs. suicide risk, b) number of previous suicide attempts (none, single vs. multiple), and c) gender (male vs. female).

D4.4.2 BCBT Procedures: Participants will receive a standard course of BCBT (12 weekly individual therapy sessions). These sessions will be completed in-person at the Providence VAMC. In rare circumstances (e.g., pandemic, extreme weather), these sessions may be provided via phone or video (VA approved VA Video Connect). When therapy sessions are conducted remotely, de-identified data may be collected by study staff at home due to remote

connection issues (due to COVID-19). Therapy is divided into three phases: orientation, skill focus, and relapse prevention. Phase one (orientation) includes developing basic self- management skills, creating a model of how suicide functions for the patient, crisis response and safety plan, treatment motivation, and developing basic emotion regulation skills. Phase two (skills focus) centers on the consolidation of emotional regulation skills, problem solving, mindfulness, and cognitive appraisal. Veterans complete worksheets and practice learned skills in session and at home. Phase three (relapse prevention) continues with skills learned in phase two but with a focus on skill generalization and maintenance. Each patient will work through all skills with a, BCBT-trained therapist. Therapy will consist of once a week, 60-minute individual therapy sessions. Participants will also be asked to complete weekly homework tasks to practice skills and strategies learned in each therapy session. Sessions will be recorded to rate therapist fidelity. To limit heterogeneity of therapy administration, if a participant is engaged in suicide-focused psychotherapy or treatment that significantly overlaps with BCBT for suicide, participants may be asked to temporarily refrain from other individual psychotherapy while receiving BCBT. However, they will be instructed to continue with all other usual mental health care (i.e. continue prescribed mental health medications and working with their mental health providers).

D4.4.2a BCBT Therapy Compliance:

The therapist will be a VA mental health counselor. The therapist will have experience and training in CBT principles and be trained and supervised by qualified research personnel to ensure training meets standards set forth in the BCBT protocol. In the event that therapy must be provided to patients via telehealth (e.g., due to pandemic, inclement weather), the therapist may provide therapy via VA-approved VVC or phone. Prior to providing therapy via these alternative means, the therapist will have completed telehealth training in TMS (4279741). Additionally, to establish the reliability and validity of the adherence and competence ratings of BCBT, therapy sessions are required to be audio recorded and will be conducted according to approved standard VA practice for audio recording research subjects (*see E. Information Security and Confidentiality Protections section for full details*). The therapy sessions will be rated by the PI (an expert in BCBT) for fidelity using a checklist from the BCBT manual.

D4.4.3 Discontinuation or Lost to Follow-Up: Participants are required to attend a minimum number of TMS sessions to assess a response. The project PI will assess each and determine how many TMS sessions each participant will require. Participants are expected to attend sessions as close to daily (during business days) as possible, completing the PI determined number of TMS visits necessary. The PI will also evaluate participants for study compliance (i.e. consistency of TMS visits) and determine if the participant may need to be discontinued from the study prior to the completion of the intervention period as appropriate.

If a participant is discontinued or lost to follow-up, the study investigator will notify the participants mental health provider about their discontinuation in the study following good clinical practice procedures.

D4.5 Intervention Endpoint Visit

The endpoint visit, if applicable, will occur at the 12th intervention therapy visit, 12 weeks (3 months) from the start of intervention. This visit will be conducted in-person, or if necessary, by telephone. When assessments are conducted remotely, de-identified data may be collected by study staff at home due to remote connection issues (due to COVID-19). Please see Table 2 for a list of scales and assessments administered at endpoint. Participants will be paid $50 in electric funds transfer (EFT) or gift cards for the completion of this visit.

D4.5 Follow-Up Visits

Follow-up assessments will be conducted in-person or if necessary, by telephone 6, 12, and 24 months from the start of the intervention period. When assessments are conducted remotely, de-identified data may be collected by study staff at home due to remote connection issues (due to COVID-19). To reduce attrition, subjects will be paid $50 in electronic funds transfer (EFT) or gift cards for completion of each follow-up appointment. Veterans participating in TMS+BCBT and neuroimaging will attend follow-up visits at 6, 12, and 24-months. Veterans only participating in TMS+BCBT will attend follow-up visits at 6- and 12-months. Veterans and matched controls participating only in the neuroimaging and cognitive battery will attend follow-ups at 6-, 12-, and 24-months.

D4.5.1 Blinded Assessment Administration: At the intervention endpoint visit, and 6-, 12-, and 24-month follow-up visits, assessments will be administered by study personnel who are blind to TMS condition (active vs. sham). For veterans who participate in the intervention component of the study, these assessments will not be administered by the study therapist or TMS provider even though they are also blind to the TMS condition. All study personnel will be blind to the study condition at baseline.

D5. Electronic Health Record (EHR) Data Extraction

Study staff will manually extract EHR data from participants' VA CPRS files. Extracted values will be entered into VA REDCap in anonymized format (by patients' study ID only). The initial data extraction will occur at baseline no later than one week of the participant's MRI Visit or beginning of intervention. Subsequent data extractions will take place six months, one year, and two years after starting intervention. At each time point (baseline, +6months, +1 year, +2 years), data for the current month, and for each of the 12 prior months will be extracted.

D5.1 EHR predictor extraction:

Participants' CPRS files will be manually reviewed by the PI or by trained study staff. The following data types will be manually extracted from CPRS files: 1) Health services utilization; 2) pharmaceutical utilization;
3) changes in pharmaceutical utilization; 4) mental health diagnoses. Factors under consideration were selected based on prior demonstrations of machine learning applied to EHR [39-41]. Related information such as names of medications and medical conditions will also be extracted.

D5.2 EHR variable construction: EHR measures are listed in Table 5. Monthly EHR sums will be averaged by quarter and by year. If categorical variables change over an aggregated time point, the most consistent designation over the analyzed epoch will be used.

Health Services Utilization
Outpatient Visits (any service)
Outpatient Visits (MH service)
Emergency or Urgent Care Visits
Inpatient MH
Inpatient (any service)
Pharmaceutical Utilization
Antidepressant
Antipsychotic
Mood Stabilizer
Anxiolytics
Other medications (non-psychiatric)
Change in Pharmaceutical
Antidepressant
Antipsychotic
Mood Stabilizer
Anxiolytics
Other medications (non-psychiatric)
Mental Health (Current and Lifetime)
Depression
Bipolar disorder
Schizophrenia or schizoaffective disorder
Generalized Anxiety Disorder
Posttraumatic Stress Disorder
Specific Phobia
Panic Disorder
Social Phobia
Personality Disorder
ADHD
SUD
Gambling Disorder
Eating Disorders
Suicidality

Table 5. EHR data extracted at baseline and follow-

E. DATA ANALYSIS

E1. Design and Sample Size

This is a single-site, two-arm RCT with individual participant urn randomization. We propose to randomize 130 Veterans. Approximately 65 will be randomized to active TMS+BCBT and 65 participants will be randomized to sham TMS+BCBT. Recruitment for the intervention will cease once randomization goals are met (i.e. n= ~65 Veterans per condition). Additionally, we will be enrolling 60 Veterans, who will be matched on age (within 5 years), primary psychiatric diagnosis, and sex, for a total of 190 Veterans to be enrolled. A subsample of these veterans (120 in total; one group (n=30) with suicide ideation and another group (n=30) with suicide attempts; and controls (n=60) will be used in the analyses of brain-based biomarkers for suicidality. Veterans will be assessed at the study timepoints outlined in C3. Assessments.

E1.1 Overall Analytic Approach across Aims

Preliminary analyses will include descriptive statistics to examine the distributional and psychometric properties of the variables (e.g., normality, internal consistency). Variables will be transformed to achieve normality if necessary. We will also examine post-inclusion attrition by comparing study completers to dropouts on sociodemographic, baseline, and length of admission data to determine if they differ systematically. Preliminary analyses may also include analyses of adverse events, progress of recruitment and retention, and quality markers as the study progresses. In keeping with the intention to treat principle, missing data will be handled with multiple imputations (m=20) with assumptions checked with sensitivity analyses [43,44] [32]. Our main analysis will not adjust for covariates other than baseline value of the outcome and design factors (balancing factors used in the urn randomization procedure) under the assumption that randomization produced groups balanced on measured and unmeasured confounders. Additionally, the data from this study across all Aims will be combined with data from subjects who completed neuroimaging procedures in PVAMC IRB protocol #2018-051.

Data from this study, across all Aims, will also be combined with data from subjects who completed procedures for PVAMC IRB protocol #IRB-2020-008.

Data from this study related to recorded interviews, de-identified with the exception of assessment dates, will also be shared with the PVAMC research study “Longitudinal Assessment of the Sleep-Suicide Link in Veterans Discharged from Inpatient Psychiatric Care” (IRB-2020-008), for training of staff and inter-rater reliability analysis (i.e., to calculate agreement across interviewers and to make final decisions on ratings).

E2. Aim 1 Analytical Plan (Analyses Related to Treatment)

The data from this study for Aim 1 may be combined with data from subjects who completed neuroimaging procedures in PVAMC IRB protocol #2018-051.

Data from this study, for Aim 1 may also be combined with data from subjects who completed procedures for PVAMC IRB protocol #IRB-2020-008.

E2.1 Interim analysis and early stopping of treatment

We will conduct 1 interim analysis and assess our primary aim when we have enrolled 32 persons per treatment group (~50% enrollment). The analyst and investigators will be blinded to treatment assignment in the interim analysis. We will test our a priori hypotheses and suggest consideration of early stopping to the DSMB if either group shows an effect on the primary outcome using O'Brien-Fleming stopping bounds [45] (i.e., a significance level of 0.0054). We will retain a significance level of 0.049 for our primary hypothesis at project completion.

E2.2 Primary hypothesis

We hypothesize that compared to sham TMS+BCBT, Veterans receiving active TMS+BCBT will demonstrate superior improvements in suicidal ideation and fewer suicide attempts. Our primary outcome for this aim is a composite measure of suicide behavior based on occurrence of any of five types of suicidal behavior: death by suicide, suicide attempt, interrupted or aborted attempts, and suicide preparatory acts. This composite score is derived from the Columbia Suicide Severity Rating Scale (C-SSRS). The C-SSRS captures data on number of attempts, aborted attempts, and interrupted attempts. Number of suicide behaviors will be added across these categories to yield a total suicide events score. Death by suicide will be captured by review of medical records and death records. The main exposure variable of interest is the random treatment assignment. Our analytic approach will be an ANCOVA-type mixed effect regression model [72]. This means the outcome composite measure at follow-up time points (e.g., 3, 6, 12 months) will be regressed on baseline value of the outcome, design factors, and treatment assignment, dummy variables for time (baseline as reference) and interactions of treatment assignment and time dummies. Random intercepts and exchangeable error covariance structure will accommodate non-independence of observations owing to the repeated measures design.

The main effect of TMS as adjunctive to BCBT will be tested with the main effect of group assignment to the joint intervention condition. The time effect interactions of TMS assignment test hypotheses about the maintenance of gains at 3, 6 and 12 months. Our main hypothesis is that there is an immediate beneficial effect of TMS exposure. For our secondary outcome, (time to first suicide attempt over 12 months) we will use a Cox proportional hazards model analysis framework.

E2.2.1 Statistical power and sample size for our primary outcome: With 65 persons per group, Lehr's equation [73] instructs that minimum detectable standardized mean difference effect size difference (d) between treatment groups at the baseline assessment is sqrt(16/n), where n is the per-group sample size, or 0.50 standard deviation units, a medium effect size in Cohen's effect size taxonomy [74]. Given the ANCOVA design, we will be able to detect a smaller effect depending upon the magnitude of the pre-post correlation (r) of the suicidal behavior composite outcome {d = sqrt([16(1-r^2)]/n}, which under the assumption of a moderate correlation (r = .2) the minimum detectable effect size is d = .47. These are medium or typical effect size magnitudes [75] and are likely to describe effects of minimal clinical significance or practical importance. Of note, these are also comparable with prior TMS studies [64,65] who described effect sizes of .5-.52, and more recent studies indicating larger (d=.9) effect sizes of TMS used with medications [76]. While we recognize these are effect sizes for depressive symptoms, in our pilot work we found reduction in depressive and suicide-related symptoms to be highly correlated. For our secondary outcome, we used simulations to determine the minimum detectable difference. If we assume that 21% of the sample will experience a suicide attempt over 12 months follow-up, if the cumulative risk of suicide attempt is 4.5% over 12 months in the TMS+BCBT group (hazard ratio = 0.19) we

will have 81.1% power to detect such an effect using a type-I error rate of 5% in a Cox proportional hazards model framework.

E2.3 Secondary hypotheses

For this aim we hypothesize, compared to sham TMS+BCBT, Veterans who receive active TMS+BCBT will have superior improvements in psychosocial functioning and fewer psychiatric hospitalizations/crisis visits during the follow-up period. The outcomes for this aim are a)

WHODAS score b) number of psychiatric hospitalizations/crisis visits c) reduced suicide ideation as measured by the C-SSRS. The analysis for the psychosocial functioning outcome, (a), and the suicidal ideation severity score from the C-SSRS, (c), will be a repeated measures ANCOVA, as with the primary hypothesis, using a generalized linear mixed effect model. For part (b), the outcome will be a count variable, for which we will use negative binomial regression.

E2.3.1 Statistical power and sample size considerations: Sample size considerations for part
(a) are similar to the primary hypothesis, and the minimum detectable effect size difference is a standardized mean difference of 0.5SD units. Without pilot data on the number of hospitalizations/crisis visits, it is difficult to forecast the distribution and detectable difference in distribution on the count outcome (part b). Rules of thumb provided by Van Belle [77] suggest we will be able to detect a relative rate of exp(4/sqrt(n)), where n is the per-group sample size, or a reduction in the rate of hospitalizations of about 61% or more among those receiving active TMS+BCBT plus versus sham.

E2.4 Moderator and mediator effects
In addition to the above hypotheses, we will conduct exploratory latent growth curve analyses to compare the trajectory of change for primary, secondary, and tertiary outcomes (i.e. linear ascending, descending, or quadratic) between sham TMS+BCBT versus active TMS+BCBT. We will include moderator variables in these models (e.g. diagnosis, comorbidity, gender), which may identify patients who will benefit more or less to the addition of active TMS+BCBT versus sham TMS+BCBT. We also will investigate mediating variables to determine the mechanisms through which TMS produces its effects on clinical outcomes**.** The set of analyses in this aim are motivated by [78], who suggest exploratory, hypothesis generating analyses be conducted after primary study aims are addressed to attempt to decide for which sample sub-groups the intervention might be more efficacious or have more lasting effects. The analytic approach will be like that described for the primary and secondary aims, although in addition to the timepoint effect indicators, we will examine models with more parsimonious time structure (e.g., linear, piecewise linear, negative exponential) and then attempt to describe factors that predict variations in important components of the implied change trajectory. We will make use or generalized linear mixed effect models and compare alternative time bases using information criteria before adding covariates, mediators, and moderators. Treatment effect mediation will be evaluated by comparing treatment effects estimated before and after adjusting for the main effect of putative mediators. Moderation effects will be examined as three-way interactions of the putative moderator, treatment assignment, and time.

> *E2.4.1 Statistical power and sample size considerations:* As we view tertiary analyses as exploratory and hypothesis generating, we do not present a priori specified sample size or minimum detectable effect size statistics. We have no doubt that we may be underpowered to detect all but large moderation effects. Our inferences will be made cautiously and be guided

by confidence intervals obtained by bootstrap resampling of the observed data.

E3. Aim 2 Analytical Plan (Analyses Related to Cognition and Neuroimaging)

All de-identified data from this study for Aim 2 will be combined with data from subjects who completed neuroimaging procedures in PVAMC IRB protocol #2018-051.

E3.1 Evaluate the relationship between STBs and reward circuits involved in decision-making in Veterans.

Hypothesis: Neural and behavioral correlates of decision-making will differentiate Veterans with STBs from those without STBs.

Rationale: Suicidality is associated with maladaptive decision-making. Neuroimaging in non-Veterans has shown that STBs are accompanied by functional and anatomical differences in the striatal-to-VMPFC reward circuit implicated in decision-making. It is unknown if these potential neurocognitive markers of suicide generalize to Veterans. Between-group contrasts of decision-making, structural MRI, and functional MRI will be used to test our hypothesis.

E5.1 Participant groups: The STB group will be comprised of Veterans hospitalized for suicide attempt (up to n=30) or suicidal ideation (up to n=30). The diagnosis matched control group is comprised of Veterans (up to n=60) without current STBs. Per power estimations computed with G Power software[42], 85% power to detect a medium-sized effect of group (0.4) in an ANCOVA model with three groups and two covariates is afforded by a total sample size of 72, or n=24 participants per group. Our enrollment targets exceed this estimate to account for loss of participants that are unable to complete all aspects of the study.

Data sources: Decision-making tasks include the scanned reward expectancy task (card guessing), and the un-scanned Iowa Gambling and Monetary Choice (Delay Discounting) tasks. Structural MRI and diffusion MRI data. FMRI data used in Aim 1 analyses will come from either the card guessing reward task or resting state functional MRI runs.

General statistical details: Age and sex will be treated as covariates of no interest in all statistical analyses. Intracranial volume (computed by Freesurfer) will also be used as a nuisance covariate in morphometry analyses to control for size-related variance. Residual effects of motion on functional connectivity estimates will be tested post hoc by regressing individuals' frame-to- frame motion against

functional connectivity beta values [55]. Potential effects of impulsivity, depression, anxiety, and sleep on outcomes will be explored in post hoc sensitivity analyses.

Behavioral Data Analysis:

PhenX Toolbox Monetary-Choice Questionnaire[43]: The protocol is scored by calculating where the respondent's answers place him or her amid reference discounting curves; placement amid steeper curves indicates higher levels of impulsivity. Subject-specific discounting rates will be entered into MATLAB ANCOVA models testing group differences.

PhenX Toolbox The Iowa Gambling Test™ [4]: Total winnings and the ratio of high vs. low risk gambles will be entered into MATLAB ANCOVA models testing group differences.

MRI Analyses: Analyses for primary hypothesis testing will employ a region of interest (ROI) approach. ROIs in VMPFC, orbitofrontal cortex, and the striatum will be used in structural and functional neuroimaging analyses. Cortical ROI definitions will be based on the Human Connectome Project multi-modal parcellation atlas [81]; subcortical ROIs will be based on Freesurfer automated parcellations. ROI analyses will be considered significant at the two-tailed alpha of $p < .05$ after Bonferroni-correction for the number of ROI comparisons. We may also conduct exploratory voxel-level fMRI analyses. These analyses will be corrected for multiple

comparisons by applying a voxel-height threshold of $p<.001$, and a cluster-size threshold of p- FDR<.05 to all second-level models.

Grey matter comparisons between Veterans exhibiting STBs and matched controls.

Cortical thickness and grey matter volume (as computed by Freesurfer) will be extracted from the VMPFC and striatum. Measures will be compared between Veterans with STBs and matched controls to test the hypothesis that these metrics are reduced in Veterans with STBs.

Differences in white matter integrity between Veterans with STBs and controls.

Deterministic tractography of diffusion data will be conducted with DSI Studio (http://dsi- studio.labsolver.org/). The generalized q-sampling algorithm will be used for fiber reconstruction. This algorithm permits estimation of multiple fibers per voxel improving reconstruction accuracy in areas rich in crossing fibers [82]. Fiber streamlines will be estimated from "seed" ROIs and then filtered to exclude streamlines passing through, but not ending in, target ROIs. If the seed is in striatum, targets will be located in VMPFC/orbitofrontal cortex, or vice versa. To test the hypothesis that white matter pathways connecting VMPFC-to-striatum are compromised in Veterans with STBs, individual-level track statistics (anisotropy, density) will be entered into MATLAB ANCOVA models.

Differences in fMRI activation during decision-making between Veterans with/out STBs.

These analyses test the hypothesis that neural signals in the striatal-to-VMPFC circuit related to rewards and decision-making are attenuated in Veterans with STBs. Preprocessed fMRI data from the reward expectancy task will be used for these analyses. Whole-brain first-level fixed-effect GLMs will be constructed for each subject with SPM12. A parametric regressor will be used to model univariate fMRI activation related to reward expectancy.
Parametric values are set to +0.5 for probable wins, –0.375 for probable losses, +0.125 for ambiguous cues, and zero for the neutral cues (see *D5.5.2*) [83]. Separate regressors for positive (better than expected) and negative (worse than expected) prediction errors will also be constructed. GLMs will be created by convolving the canonical hemodynamic response function with regressors of interest and nuisance regressors (motion parameters and derivatives, mean signal in cerebrospinal fluid). Subjects will be treated as random effects in second-level univariate fMRI models. To evaluate whether reward-related signals are blunted in Veteran with STBs, the averaged blood oxygen level-dependent (BOLD) signal for our conditions of interest will be extracted from VMPFC and striatal ROIs and contrasted between groups. Whole-brain statistical maps for reward expectancy and prediction errors will also be contrasted between Veterans with STBs and controls.
Statistically significant clusters from this univariate whole-brain analysis may be used as ROIs in functional connectivity models below.

Differences in functional connectivity between Veterans with STBs and controls.

These analyses test the hypothesis that the VMPFC-to-striatal decision-making circuit is less functionally cohesive in Veterans with STBs. Functional connectivity analyses of both task (reward expectancy) and resting-state will be conducted using the CONN Toolbox.[50]

Unsmoothed residual BOLD time courses will be extracted from each subjects' preprocessed data and then cross-correlated. The resulting correlations will be converted to z-scores via Fisher's R-to-Z transformation in order to improve conformation to the assumptions of the GLMs used for seed-based hypothesis testing. Z-scores will be entered into GLMs comparing VMPFC-to-striatal connectivity between groups. For task-based functional connectivity, a weighted GLM approach will be used to compare connectivity during the expected reward and prediction error task conditions of between Veterans with and without STBs. Additional analyses using ROIs functionally-defined in the univariate analysis described above as seeds may also be run.

Design Considerations & Alternative Outcomes: This hypothesis testing sequence focuses on the VMPFC-to-striatum decision-making circuit. However, effects may be mediated by regions outside this *a priori* network e.g. in the amygdala-to-VMPFC circuit implicated in bipolar disorder with suicidality [85]. The role of this circuit could be explored should we fail to reject the null hypothesis. Alternatively, a data-driven method such as multi-voxel pattern analysis could be used to functionally identify neural circuits differing between Veterans with and without STBs.

E3.2 Evaluate whether correlates of decision-making and cognitive control indicate risk severity.

Hypotheses: Decision-making will be less risky and/or impulsive in higher- vs. lower- risk Veterans with STBs. Structural and functional integrity of cognitive control regions will be superior in higher-risk Veterans with STBs.

Rationale: Studies comparing decision-making between individuals who have made high-risk (well-organized, highly lethal) attempts vs. those making less organized or less medically serious attempts have found that decision-making is less impulsive in higher- risk attempters [86]. In fact, decision-making in high-risk attempters is even less impulsive than it is in healthy controls. Some propose that the capacity to make a serious suicide attempt develops alongside the ability to inhibit prepotent pain and fear responses associated with death [87]. Thus, paradoxically, greater inhibitory cognitive control may facilitate development of suicidal behavior. As a test of this hypothesis, we will compare behavioral and functional neuroimaging data collected during the SSRT, an inhibitory cognitive control task, between high- and lower-risk Veterans with STBs. We will also examine associations between suicide and other cognitive control measures to assess the specificity of the link between attempts and inhibitory control. to assess the specificity of the link between attempts and inhibitory control.

Participant groups: The high-risk group will be comprised of Veterans with history of suicide attempt (up to n=30), while the low-risk group will include Veterans with ideation only (up to n=30). See alternative methods for risk grouping in the Design Considerations section below. Diagnosis matched controls (up to n=60) are also used in some analyses.

Data sources: Structural data (cortical thickness and volume) and diffusion MRI data. FMRI data used in Aim 2 analyses will come from either the SSRT, the scanned decision-making task, or resting state runs. Behavioral measures of decision-making include data from the scanned decision-making task. Behavioral measures of cognitive control include data from the scanned SSRT, and the un-scanned Intra-Dimensional Card Sort and Flanker tasks.

General statistical details: Age and sex will be treated as covariates of no interest in all statistical analyses. Intracranial volume (computed by Freesurfer) will also be used as a nuisance covariate in morphometry analyses to control for size-related variance. Residual effects of motion on functional connectivity estimates will be tested post hoc by regressing individuals' frame-to- frame motion against functional connectivity beta values [55]. Potential effects of impulsivity, depression, anxiety, and sleep on outcomes will be explored in post hoc sensitivity analyses.

Behavioral Data Analysis:

NIH Toolbox Dimensional Change Card Sort Task: Accuracy and reaction time scores will be computed for each subject (both raw and age-adjusted); higher accuracy and lower reaction times are associated with greater cognitive flexibility. Subject-specific scores will be entered into MATLAB ANCOVA models testing group differences.

NIH Toolbox Flanker Inhibitory Control and Attention Test: Total winnings and the ratio of high vs. low risk gambles will be entered into MATLAB ANCOVA models testing group differences.

MRI Analyses: Analyses for primary hypothesis testing will employ a region of interest (ROI) approach. ROIs in the cognitive control areas of ventrolateral PFC (VLPFC- pars orbitalis, pars triangularis, pars opercularis), dorsolateral PFC (DLPFC-approx. Brodmann's Areas 46/9), and anterior cingulate (ACC-rostral and dorsal) will be used in structural and functional neuroimaging analyses. Striatal ROIs will also be tested as they are part of thalamo-cortical loops that include control regions [89]. Cortical ROI definitions will be based on the Human Connectome Project multi-modal parcellation atlas [90]; subcortical ROIs will be based on Freesurfer automated parcellations. ROI analyses will be considered significant at the two-tailed alpha of $p < .05$ after Bonferroni-correction for the number of ROI comparisons. We may also conduct exploratory voxel-level fMRI analyses. These analyses will be corrected for multiple comparisons by applying a voxel-height threshold of p<.001, and a cluster-size threshold of p- FDR<.05 to all second-level models.

Grey matter comparisons between groups. Anatomical differences in cognitive control regions may contribute to poor cognitive control and the decision-making impairments observed in non-attempters relative to attempters and controls. As a test of this hypothesis, cortical thickness and grey matter volume in cognitive control regions (extracted with Freesurfer) will be compared between high-risk Veterans with STBs, low-risk Veterans with STBs, and controls. Morphometry statistics will be entered into GLM group contrasts for each ROI.

Differences in white matter integrity between groups. PFC regions involved in cognitive control are anatomically connected to striatum by white matter pathways, e.g. the cortico- striato-thalamic loops[2]. Damage to these pathways may undermine efficient neurotransmission of top-down cognitive control signals which are fundamental for goal- directed behaviors including decision-making[5]. In individuals with STBs, efficiency of the cognitive control system may permit the development of more deliberate suicidal behaviors rather than impulsive attempts. Deterministic tractography statistics will be contrasted between groups to test this hypothesis. Tractography procedures match those used above (*Differences in white matter integrity between Veterans with STBs and controls).* Subjects' track statistics (anisotropy, track density) will be entered into GLMs contrasting high-risk and low-risk Veterans with STBs.

Univariate fMRI differences in inhibitory control. This analysis tests the hypothesis that response inhibition, a component of cognitive control, will be superior in high-risk Veterans relative to their lower-risk Veterans and controls. We anticipate that the fMRI signal in VLPFC during successful inhibition will be strongest in the high-risk group relative to lower-risk Veterans with STBs and controls.

Preprocessed SSRT will be entered into subject-level fixed-effect GLMs constructed with SPM12. Regressors for the following trial types will be constructed: Go trials, Stop Inhibit trials, Stop Respond trials, along with two nuisance regressors (go errors, non- response trials). Stop-Inhibit and Stop Respond trials represent successful, and unsuccessful attempts to halt responses in progress. Null events constitute an implicit baseline. GLMs will be created by convolution of the canonical hemodynamic response function with model regressors. Motion estimates and mean signal in cerebrospinal fluid will also be included as nuisance regressors. Contrasts for each trial type and Stop Inhibit– Stop Respond trials will be included in first-level models. Second-level models where subjects are treated as random effects will be estimated by regressing first-level contrast betas against group. Averaged betas across voxels from ROIs will also be extracted from each subject and contrasted between groups to conduct ROI-level hypothesis tests.

Adaptive decision-making and inhibitory control. Here, we will test the hypothesis that high-risk Veterans' superior capacity for inhibitory cognitive control enables less impulsive decision-making. Separate GLMs will be constructed predicting either delay discounting (Monetary-Choice Questionnaire), or the proportion of risky choices (Iowa Gambling Task). Predictor variables include Group (high-risk, low-risk, controls) and Inhibitory Control (stop signal reaction time), Impulsivity (BIS-11 or alternatively, UPPS scores), or fMRI activation during correct inhibit SSRT trials. Follow-up control analyses in which the performance metrics from the Dimensional Card Sort and Flanker Tasks (see Research Plan – Methods and measures) are substituted for the Inhibitory Control measure will be conducted to determine if risk is specifically related to inhibitory control or is a by-product of generally better cognitive control.

Resting-state functional connectivity in the cognitive control network and its relationship to decision-making. Greater functional cohesion amongst ROIs in cognitive control networks is associated with better cognitive control performance [62]. Greater activation in cognitive control regions is also associated with decisions that promote long-term goals [92]. Thus, correlations between cognitive control ROIs may be stronger in high-risk suicidal Veterans given that their better decision-making performance may be due in part, to superior cognitive control. Functional connectivity analyses will be conducted using the CONN Toolbox and according to methods outlined in D9. The GLM testing logic follows the sequence above in Analysis D10.5.5, however, beta values describing functional connectivity amongst ROIs in the control network

for each subject will be used to predict Monetary Choice and Gambling performance.

Design considerations & alternative strategies for Aim 2. This design uses a categorical factor to define groups that approximates risk by history of attempt versus ideation, based on the strength of previous attempt as a risk factor for subsequent attempts. While straight-forward, we acknowledge that within-group heterogeneity may invalidate this grouping strategy. For instance, the ideation group could contain a significant number of Veterans with highly detailed suicide plans that have begun obtaining means that would be better classified as high-risk. In recognition of this issue, we will also compute empirically-determined risk categorization thresholds based on Beck Lethality Scale, Suicide Intent Scale, and Scale for Suicide Ideation scores. Alternatively, we may use continuous variables operationalizing suicidal planning, intent, or lethality for these analyses.

E3.3 (Exploratory) Integrate EHR data and neurocognitive markers into predictive models of STBs.

> We will combine EHR data and objective cognitive measures forming a high- dimensional, multi-modal dataset. Machine learning algorithms will be applied to examine the predictive utility of this approach.
>
> Rationale*:* Machine learning algorithms can accommodate large predictor sets and can model complex interactions among factors. Models built on EHR outperform traditional models with predictive accuracy in excess of AUC +0.70. We will subject an EHR dataset enriched with additional, objective, cognitive measures of suicidality (defined in Aims 1 & 2) to machine learning classification. Three types of supervised machine learning models (described below) will be used for this exploratory analysis. Models will be constructed both with, and without, Aim 1 & 2 measures to test if their inclusion improves suicide prediction.

Data sources: Aggregated EHR data (Section D6.2) and subject-level performance outcomes on the reward expectancy scanned task, Delay Discounting task, Iowa Gambling Task, Flanker Task, Dimensional Card Sort Task, and SSRT task.

General approach: The dataset comprised of subject-level aggregated EHR variables and behavioral outcomes from cognitive control and reward tasks will be treated as a "discovery data set," meaning that it will be used to train machine-learning algorithms and make initial identifications of subsets of the dataset associated with distinct suicide outcomes. Classifier training, cross-validation, and optimization will be performed using this discovery data set. The goal is to predict participants with: 1) history of attempt, 2) suicidal ideation without history of attempt, 3) no history of STBs. Future studies will attempt to replicate findings in an independent sample.

Software: Part of this exploratory aim involves testing implementations against one another. Modeling will be carried out using Julia[64], an open-source computing language, MATLAB, and R.

Machine learning algorithms:

Elastic Net Regularized Logistic Regression [65] Unlike other regularized regression methods such as ridge or lasso, elastic net models are stable when multicollinearity amongst

predictors is high. Elastic net regularization penalizes model complexity by specifically modeling overfitting simultaneously combining the shrinkage and recovery approaches of lasso and ridge regularization. This means that coefficients are all retained but undergo shrinkage toward zero. We will use a 10-fold cross-validation to assess the performance of the classifier.

Random forest machine clustering Random forest clustering is a tree-based supervised learning algorithm that can handle high multi-collinearity and is robust to overfitting [95]. Decision trees are built by recursively subsampling predictors from the training dataset [95,96]. At each "split" of a tree, the algorithm searches for a given variable and the binary decision that splits the predictor subset. As trees are built, progressively smaller predictor subsamples are drawn and used to predict earlier data splits forming "parent" and "child" nodes. The number of predictors at each node will be determined by the square root of the total number of predictors to limit over-fitting [96] and an error minimization criterion will be applied to select the predictor and cut point at each node of the decision tree that optimizes binary splits. This iterative process will continue down the tree until node size is equal to 10% of the total study sample. A 10-fold cross-validation will also be run as a preliminary validation of estimates.

Support Vector Machines (SVM) A supervised non-linear kernel function is used to transform the input data to a high-dimensional space, wherein individual observations are plotted as points in this n-dimensional space (n=size of predictor set). Classification is performed by identifying the mapping function that maximally segregates data classes. The choice of an underlying kernel function and its parameters can be used to balance the trade- off between classifier performance and complexity of dimensional space. Probability estimates, tuning of kernel, and regularization parameters will be computed by means of cross-validation.

Model comparisons Receiver Operating Characteristics (ROC) will be used to compare accuracy of models' predictions. The area under the ROC curve statistic (AUC) will be used as the metric of algorithm classification performance, the model with the highest AUC value will be considered the best-fitting model. Models will undergo 10-fold cross-validation and bootstrap optimization analyses to measure model robustness.

Model interpretation: Although building models to predict STBs is the primary focus of this Aim, these models can yield additional valuable information that will advance our understanding of suicidal phenotypes. As post-hoc analyses, we will analyze the approach and strategy used by each of the classifiers listed above to predict STB. Different machine learning algorithms have various degrees of predictability. In Logistic Regression for example, studying the regression coefficients can provide insights about the information content of the features selected by the model for classification. Specific algorithms have been developed for other classifiers that estimate feature contribution [97]. This would lead to a

data-driven and unbiased identification of risk factors, many of which could be modifiable by simple interventions and as a result could reduce the risk of STBs.

Design considerations and alternative approaches: This study sample size is small because of budgetary restrictions. We recognize that this decreases the likelihood that models will generalize to an independent sample. A transdiagnostic participant sample is planned because

this naturalistic sample will be more representative of Veterans with STBs. Heterogeneity however, may beget misclassification errors i.e. classification by disorder versus suicidal outcome. The AUC statistic is our planned metric for model comparisons because it easily interpreted. However, AUC metrics can overestimate true performance when applied to a larger dataset where one group is comparatively over-represented i.e. a high AUC is achieved by algorithms optimizing the identification of controls over cases. Alternative performance measures that simultaneously evaluate positive predictive value and sensitivity like precision- recall statistics may be a more robust alternative to AUC.

E3.4.2 Volume-space structural preprocessing. T1-weighted images will undergo intensity normalization, tissue segmentation, and volume-space registration to the Montreal Neurological Institute (MNI)-152 Atlas.

E3.4.3 Surface-space structural preprocessing. T1-weighted images will be resampled to Freesurfer-conformed space, then submitted to intensity normalization, tissue segmentation, spherical registration, volume-space registration to the MNI-152 Atlas. Freesurfer preprocessing also includes surface-space cortical parcellation and volume-space subcortical parcellation.

E3.4.4 General fMRI preprocessing. The following preprocessing steps apply to all fMRI data. Steps include slice-time correction, head motion estimation, realignment, inhomogeneity correction via field map, functional segmentation, registration to MNI-152 space, and an artifact analysis in which high motion volumes (>0.5mm translational or 0.02 rotational motion), or volumes where global signal variance exceeds 3 standard deviations are flagged for nuisance regression in subsequent models. Spatial smoothing with a 4mm full-width, half max Gaussian kernel will be applied to fMRI data subjected to univariate analyses to improve conformation to the assumptions of Random Field Theory.

E3.4.5 Functional connectivity preprocessing. The following additional subject-level steps carried out with CONN reduce the impact of motion-related artifacts and non-neuronal signal on functional connectivity estimates [100-102]. The anatomical CompCor (aCompCor) routine (implemented in CONN) is an effective method for removing motion-related artefact that does not involve global signal regression [103], a practice that complicates interpretation of correlations [104,105]. Five principal components are extracted from the averaged fMRI signal in each aCompCor compartment (white matter, CSF). Principle components are regressed from subject-level data, along with regressors for linear trend, six estimated motion parameters and their 1st derivatives, and flagged high-motion or high global signal variance time points to limit potential sources of spurious variance. Residuals will be band-pass filtered (high-pass = 0.008, low-pass = 0.15) after confound regression [106].

E3.4.6 Diffusion MRI preprocessing: Preprocessing steps include: eddy-current compensation, head motion estimation and correction, and intra-subject registration. Diffusion preprocessing will be carried out using either FSL or FreeSurfer.

F. PRIVACY, CONFIDENTIALITY, & INFORMATION SECURITY

F1. Privacy interests and confidentiality

Minimizing risk of loss of Protected Health Information (PHI) is a priority of the proposed study. In accordance with VA guidelines and laws of the State of Rhode Island and Providence Plantations, confidentiality of the participants and their information will be upheld as outlined in this document. In agreement with the Department of Veterans Affairs Record Control Schedule 10-1, records will be maintained as outlined in this document. All documentation and data obtained over the course of this study will be stored as outlined in this document.

To protect participants' confidentiality, study participants will be assigned a numerical code that contains no personal identifiers or PHI. Participants will be listed only by this unique participant identification code on data files and data capture forms to maintain their anonymity. Codes will be sequential in numbering, e.g. 7001, 7002, 7003 etc. Identification codes will be applied to all cognitive testing, assessments, health service utilization, and MRI data collected over the course of the study.

The only documents or files containing PHI are: 1) informed consent, HIPAA documents, and demographic forms, 2) a password-protected Excel file containing contact information used for recruitment, and 3) a password-protected Excel log file linking participants to study numbers. Paper files will be stored in a locked file cabinet in a designated, lockable office in building 32. Electronic files containing PHI will be stored on a secured VA server in a restricted access folder (\\ R04pronas21\RESEARCH_PROTOCOLS\Philip\MRI_TMS+BCBT-R).

If a situation arises that is mandated by law (e.g. suspected child or elder abuse) or to ensure adherence to good clinical practice (e.g. participant in imminent medical danger and EMS is called; participant discloses intention to make an imminent suicide attempt and is taken to in-patient mental health), participants' confidentiality may be breached.

F2. Data use

Data collected from this study will be used for research purposes only. Participant-identifiable information will not be shared outside the VA. Participant-identifiable information will not be released or published without written permission unless required to do so by law. Access to participant-identifiable information is limited to researchers included in this protocol. Information that could potentially permit the identification of individual participants will not be included in publications or reports, nor will they be shared with researchers who are not members of study staff.

De-identified data (e.g. questionnaires, self-report measures, imaging data, cognitive task data, scores from interviews) with the exception of assessment dates, from this project may be shared with PVAMC protocol #2018-051 entitled "Neuroimaging of a Suicidal Thoughts and Behaviors," led by investigator Dr. Jennifer Barredo and PVAMC protocol #IRB-2020-008 entitled "Longitudinal

Assessment of the Sleep- Suicide Link in Veterans Discharged from Inpatient Psychiatric Care," led by investigators Dr. Jennifer Primack and Dr. John McGeary.
Interview data, de-identified with the exception of assessment dates, from this study may also be shared with the PVAMC protocol "Longitudinal Assessment of the Sleep-Suicide Link in Veterans Discharged from Inpatient Psychiatric Care" (IRB-2020-008) led by investigators Dr. Jennifer Primack and Dr. John McGeary. These interview recordings would be shared for training purposes. Only approved members of the study will have access to recordings containing identifiable data.

F4. De-identification of data

Data will be de-identified with a unique subject identification code being used instead of PHI being associated with the data. Identification codes will not be based on participant PHI. They will be sequential in numbering, e.g. 7001, 7002, 7003 etc.

F5. Information security training

All employees that handle data will be trained in confidentiality policies and procedures. To remain active on this study, research staff must remain up to date with VA Privacy and Information Security and Rules of Behavior training. All staff training is tracked through Talent Management System (TMS). Appropriate supervisors are selected, and expiration notices are sent to both to ensure that users are up to date. Additionally, computer access is denied if training lapses.

F6. Software & computing equipment

F6.1 VA furnished software: VA-licensed MS Office and Excel will be used for log records and staff communication. The participant ID link log will be maintained using Excel with key access. VA-licensed SPSS software may be used to organize and analyze data kept on the VA research server. Speech Exec Pro Dictate (Phillips, v11) will be used for the transfer of audio recordings from approved recording devices to the research study folder on the VA server. The software has been installed onto select study staff's computers and sanctuary requests have been granted to allow staff to connect audio devices to their VA networked computers. These resources will be accessed via standard-issue VA-networked PC workstations.

VA TRM has approved the use of Speech Exec Pro with constraints [7,8]:

[7]: Users must ensure that Microsoft .NET Framework is implemented with VA-approved baselines. (refer to the 'Category' tab under 'Runtime Dependencies')

Speech Exec software has only been installed on VA-baselined computers with a Windows operating system.

[8]: Veterans Affairs (VA) users must ensure VA sensitive data is properly protected in compliance with all VA regulations. All instances of deployment using this technology should be reviewed by the local ISO (Information Security Officer) to ensure compliance with VA Handbook 6500.

The data uploaded using the Speech Exec software is stored on the protected research server, restricted to only study staff members.

F6.2 Specialized computing workstations: These are required to carry out the neuroimaging and computational modeling analyses in this proposal approved by CSR&D (1 IK2 CX001824-01A1). Multi-core Apple Macintosh™ Super Computers (Unix operating system) will be used because most functional and structural brain imaging software packages run more efficiently on Unix.
The two Apple Super Computer used for neuroimaging analyses and computational modeling are housed in double-secured PVAMC Building #32 (rm. 149). The Super Computer is a non-VA networked, non-encrypted, multi-core Macintosh computer and high-capacity external drive. These Super Computer will be connected to internet (currently supplied by PVAMC bldg. 32 Cox small business account), but not the VA intranet. Due to size and amount of neuroimaging data produced for each participant, dat

encryption is used due to errors produced by encumbered input output (I/O) function. Only de-identified data will be analyzed or stored on these non-networked, non-encrypted VA workstations. The super computer will have unique administrator and user accounts. Administrator accounts will not have access to Web Email. External data storage drives (not encrypted) will be partitioned for backup of Apple Super Computer. Super Computer and administrator accounts will be maintained and managed by the Neuroimaging and Scientific Computing Core (see attached SOPs). See Figure 3 for device EE numbers and locations.

F6.3 Software for super computer workstations: Super computers will be outfitted with general purpose and specialized scientific software necessary for the neuroimaging analyses and computational modeling aims of CSR&D (1 IK2 CX001824-01A1).

Details of package origins and usage provided below. Open-source software is available for download from the NeuroImaging Tools and Resources Collaboratory (NITRC), or from academic neuroimaging repositories.

*Denotes Brown licensed software. **Software to be installed with Homebrew.

MATLAB* (R2020b) (https://www.mathworks.com/products/matlab.html)

MATLAB is a commercial mathematical software package used for analysis, modeling, and algorithm development. MATLAB is a dependency of several neuroimaging software packages (Freesurfer, SPM, FSL). Although VA does have an institutional license for MATLAB, the available VA version of MATLAB is several versions behind the current stable version causing compatibility problems with software dependent on MATLAB. MATLAB will be downloaded through Brown University license.

MRIcron (https://www.nitrc.org/projects/mricron)

MRIcron is a suite of neuroimaging programs developed at the McCausland Center for Brain Imaging used for image viewing and conversion of dicom format images (the 'raw' format on data DVDs) to compressed files or NifTI images (also referred to as .nii files). Download available through NITRC from above link.

OsiriX (http://www.osirix-viewer.com/)

Alternative neuroimaging viewing software. OsiriX has a commercial and a free version, the freeware version is used here. OsiriX can be used to view images that have not been converted into .nii files which can be useful if errors occurred while data was being written to DVD. Not available at VA, download without charge from above link.

Statistical Parametric Mapping (SPM12)
(http://www.fil.ion.ucl.ac.uk/spm/software/spm12/)

The SPM software package is used for the analysis of brain imaging data sequences. The sequences can be a series of images from different cohorts, or time-series from the same subject. The current release is designed for the analysis of fMRI, PET, SPECT, EEG and MEG. Developed by researchers at University College London. Not available at VA, download without charge from above link.

CONN: Functional Connectivity Toolbox
(https://www.nitrc.org/frs/?group_id=279)

CONN is a Matlab-based cross-platform software for the computation, display, and analysis of functional connectivity in fMRI (fcMRI). CONN includes a rich set of connectivity analyses (seed-based correlations, ROI-to-ROI graph analyses, group ICA, masked ICA, generalized PPI, ALFF, ICC, GCOR, LCOR, etc.) in a simple-to-use and powerful software package. CONN is available for resting state data (rsfMRI) as well as task-related designs. It covers the entire pipeline from raw fMRI data to hypothesis testing. Developed by researchers at Harvard/MGH. Not available at VA, download without charge from above link.

XQuartz (https://www.xquartz.org/)

XQuartz is an open-sourced graphic system for Unix(Mac OS) machines and is a Mac OS compatible version of X11. XQuartz is a dependency program for several neuroimaging programs including, but not limited to, AFNI and FSL. Not available at VA, download without charge from above link.

FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FslInstallation)

FSL is a comprehensive library of image analysis and statistical tools for FMRI, MRI and DTI brain imaging data. FSL is written mainly by members of the Analysis Group, FMRIB, Oxford, UK. Not available at VA, download without charge from above link.

Analysis of Functional Neuroimaging (AFNI) (https://afni.nimh.nih.gov/pub/dist/doc/htmldoc/background_install/download_link s.html#b-downloading-a-set-of-the-newest-precompiled-afni-binaries)

AFNI is a set of C programs for processing, analyzing, and displaying FMRI data. It runs on Unix+X11+Motif systems, including SGI, Solaris, Linux, and Mac OS X. Funded and maintained by researchers at NIH. Not available at VA, download without charge from above link.

FreeSurfer (https://surfer.nmr.mgh.harvard.edu/fswiki/DownloadAndInstall)

FreeSurfer is a software package for the analysis and visualization of structural and functional neuroimaging data from cross-sectional or longitudinal studies. It is developed by the Laboratory for Computational Neuroimaging at the Athinoula A. Martinos Center for Biomedical Imaging. It is the gold-standard software package for conducting 2D surface-based analyses. FreeSurfer is the structural MRI analysis software of choice for the Human Connectome Project. Not available at VA, download without charge from above link.

Artifact Detection Tools (https://www.nitrc.org/projects/artifact_detect/)

Toolbox for post-processing fMRI data. Includes software for comprehensive analysis of sources of artifacts in timeseries data including spiking and motion. Most compatible with SPM processing, but adaptable for FSL as well. Not available at VA, download without charge from above link.

Connectome Workbench (https://www.humanconnectome.org/software/get- connectome-workbench). Connectome Workbench is an open source, freely available visualization and discovery tool used to map neuroimaging data, especially data generated by the Human Connectome Project. The distribution includes wb_view, a GUI-based visuali

wb_command, a command-line program for performing a variety of algorithmic tasks using volume, surface, and grayordinate data. wb_command is necessary for running HCP data processing pipelines. Not available at VA, download without charge from above link.

R and RStudio (https://www.r-project.org/) R is a free software environment for statistical computing and graphics. Available through VA or at the above link used to conduct nightly updates to R on the VA VINCI server.

Julia (https://julialang.org/) A specialized programming language appropriate for scientific computing and intensive computational modeling applications. Developed and maintained by the Massachusetts Institute of Technology. Not available through VA, but can be downloaded without charge at the above link.

SPSS v26* IBM SPSS platform for advanced statistical analysis. Available via the VA, albeit for an out-of-date version (v21). Up-to-date version has been downloaded at no cost to VA through the academic licenses associated with Brown University.

Python. (https://www.python.org/). Versions 2.7 and 3.8. A programming language that integrates several neuroimaging processing and analysis packages. Both versions are required for different software. Python2.7 is already installed on MacOS operating systems. To install Python 3.8 using the bash shell and Homebrew, use the following:

< brew install python@3.8 >

PIP3 (https://pip.pypa.io/en/stable/). Python package installer / manager. Not available at VA. To install pip, use <python3 get-pip.py> or <python3 get-pip.py –user>. In order to upgrade pip <pip3 install -U pip>.

Apsera Connect Browser Plugin (https://www.ibm.com/products/aspera/downloads?list). Browser plugin used for downloading freely available Human Connectome Project data. Not available at VA, download without charge from above link.

Heudiconv (0.9.0) (https://heudiconv.readthedocs.io/en/latest/usage.html). Heudiconv is a python-based dicom to BIDS converter. Not available at VA. To install heudiconv fom the bash shell using python, use the following:

< pip3 install heudiconv[all] >

Docker (https://www.docker.com/products/docker-desktop) is an application used to build containerized software that can be used to update MRIQC and FMRIPrep image processing pipelines. Install from a disk image downloaded from Docker's website.

MRIQC (0.16.0) (https://mriqc.readthedocs.io/en/prepare-release/about.html). MRIQC is a neuroimaging program that extracts quality assurance information from structural and functional MRI data. It is open-source software developed by the Stanford Center for Reproducible Neuroscience. Not available at VA. MRIQC can be used by pulling the latest docker image < poldracklab/mriqc:latest >.

fMRI Prep (20.2.1) (https://fmriprep.org/en/stable/). fMRI Prep is a preprocessing pipeline developed by the Poldra

Center for Reproducible Neuroscience. fMRIPrep can be used by pulling the latest docker image < poldracklab/fmriprep:latest >.

Bids-validator (https://github.com/bids-standard/bids-validator). BIDS-validator will validate any BIDS datasets. To install via python use:

< pip3 install bids_validator >

DSIStudio (http://dsi-studio.labsolver.org/). DSI Studio is a tractography software tool used ot map brain connections and correlations. It is freely available from the link above and was developed by Frang-Cheng Yeh. Not available at VA, download without charge from above link.

Java (java.com). Java is a programming language and computing platform. It is a dependency software for the NIH NDA GUID tool. Not available at VA, download without charge from above link.

Adobe Creative Cloud

A software suite for non-medical image processing. Includes Photoshop and Illustrator which are used for creation of publication quality graphical images used for dissemination of VA research in peer-reviewed publications, national meetings, and when approved, press releases.

F7. Web applications

F7.1 VA REDCap: REDCap is a web-based application and electronic data capture tool enabling VA users to securely collect and store research data. VA REDCap will be used to store de-personalized information from assessments, interviews, and computerized behavioral testing data. De-personalized data will be uploaded from text files imported to VA workstations via a VA-encrypted USB or manually entered by study staff.

F8. Data flow

See Figure 3 for illustration of devices involved in data collection processing and storage. The following data will be collected at each stage of the study:

F8.1 Pre-Screening and Recruitment: Contact information for potential study participants will be collected during CPRS chart reviews, clinician referrals, or during in-person or telephone contact prior to initial screening. These data will be used for recruitment of potential participants via an initial letter and subsequent phone call. These data will be kept in password- protected Excel spreadsheets stored in a restricted study database located on a secure, VA- networked server behind the VA firewall.

F8. 2 Study Enrollment: Data on paper and digitally recorded audio data will be generated during initial in-person evaluations for study enrollment which will occur at the PVAMC. Study staff will administer informed consent and HIPAA paperwork per PVAMC IRB-approved procedures to all potential participants. These documents, which contain PHI, will be physically transported by study staff in an opaque folder with a fastener to the designated lockable office in double-secured bldg. 32. Study staff will also scan consent and HIPAA forms into CPRS per standard PVAMC research procedures.

Eligibility evaluations will take place on the in-patient psychiatric units, in-patient medical units being used to treat psychiatric patients, or in office space dedicated for clinical interviews in Bldg. 32, room 143. These evaluations are used to confirm suicidality and diagnostic information

Paper copies of screening forms used during inclusion/exclusion evaluation will be labeled with de- identified subject numbers only. Forms will be stored in a locked cabinet accessible only by study staff in PVAMC Bldg. 32, rm. 143. Digital audio recordings of interviews during screens will be uploaded to a restricted folder on the secure VA research server immediately after the session. Digital audio recordings are used to enable scoring by a second rater (IRB approved study staff) in ambiguous cases e.g. level of suicidal intent is unclear. Recordings will be uploaded to a restricted folder on the secure VA research server immediately after the session and will be erased from the digital voice recorder after upload.

Data about VA health care utilization (e.g. number of primary care visits in the year prior to enrollment) will be extracted from participants' CPRS files if they meet enrollment criteria and give informed consent. CPRS data will be de-personalized during data extraction and entered into VA REDCap. De-identified data may be exported from REDCap and transferred to Apple Super Computers via VA-encrypted hard drive for further analysis. These computers are outfitted with software packages that are unavailable through the VA (see above), but are necessary for computational modeling.

F8.5 Baseline, Endpoint, and Follow-ups: Digital voice recordings collected during interviews will be recorded. Recordings will be uploaded to a restricted folder on the secure VA research server immediately after the session and will be erased from the digital voice recorder after upload. Data on paper generated during follow-up will be labeled with de-identified subject numbers only. Forms will be stored in a locked cabinet accessible only by study staff in PVAMC Bldg. 32, rm. 143. Data about VA health care utilization extracted from participants' CPRS files at follow-up, de-personalized during extraction, and entered into VA REDCap. De-identified data may be exported from REDCap and shared with study staff via VA-encrypted USB for analysis on research-owned, non-encrypted, password-protected Apple Super Computer and external drive/file serves in PVAMC bldg. 32, rms. 150 and 143.

F8. 3 MRI and Cognitive Battery Visit: Cognitive tasks will be administered at PVAMC on non- networked, non-encrypted research-owned computing devices (non-VA networked Apple iPad). The NIH Toolbox application will be downloaded to iPad and used for cognitive testing. Use of NIH common data elements in the NIH Toolbox requires the use of iPads for test administration. For additional NIH Toolbox information see: http://www.healthmeasures.net/index.php?option=com_content&view=category&layout=blog &id=150&Itemid=844. Cognitive testing data will be collected using subject ID numbers only. De-identified raw task data stored by subjects' unique participant numbers will be transferred to Apple Super Computers via VA-encrypted hard drive. Cognitive measures may be incorporated into imaging analyses conducted on Apple Super Computers. These computers are outfitted with software packages that are unavailable through the VA, but necessary for analyses. Final summaries of these analyses in Excel spreadsheets or Word documents will be transferred to the VA network via encrypted hard drive and saved on the secure VA research server.

Magnetic resonance imaging (MRI) data will be gathered at the PVAMC imaging facility in Building 1. Raw/original imaging data is collected in de-identified format using only participant ID numbers. MRI data will be transferred from the PVAMC MRI acquisition computer to the PI's AEGIS Fortress L3 encrypted hard drive. (Please see attached SOP for all details related to the hard drive). Following the secure transfer of data from the MRI acquisition comp

drive, data will be transferred to two separate computers. First, the MRI data will be transferred from the hard drive to the PVAMC Research server (the PI's secure folder: \\r04pronas21.v01.med.va.gov\RESEARCH_PROTOCOLS\Barredo\NSTB-R). Secondly, the MRI data will be transferred from the hard drive to the designated Apple Super Computer for analysis. As raw imaging data is neither saved nor stored on the PVAMC MRI acquisition computer, a copy of the MRI data will be made to back-up raw imaging data. This copy will be kept in a locked file cabinet in Building 32, Room 149. Once it has been verified that the MRI data is securely stored on the PVAMC research server and a back-up CD/DVD copy of the data has been made, the Aegis hard drive will be reset which erases all stored data.

MRI data are recorded in Digital Imaging and Communications in Medicine (DICOM) standard format. DICOM image files are large. DICOMS will be converted into the more compact NIH-standard Neuroimaging Informatics Technology Initiative (NiFti) format during download onto Apple Super Computers. Any PII in the DICOM metadata headers (e.g. dates) are removed during the conversion to NiFti files. NiFti files will not contain any identifiable information. Conversion is executed with custom scripts built on software written by the PI. Secondary files created during neuroimaging analyses on Apple Super Computers will be stored on Apple Super Computer partitioned external drives. These partitioned external drives allow for redundant storage of imaging data. Analytical results and secondary files will remain de-identified.

Cognitive tasks will be administered during MRI scanning at PVAMC on a non- networked, non-encrypted research-owned Apple laptop. Use of the non-networked laptop facilitates the use of custom code for cognitive tasks built with software unavailable at the VA (outlined above). Cognitive task data will be collected using subject ID numbers only. Cognitive data will be transferred via encrypted hard drive: 1) to the VA network stored in a restricted folder on the research server, and 2) to Apple Super Computers. Study staff will also import transferred cognitive testing data on the VA research server into VA REDCap providing a second back-up.

F8.6 Analyses on Brown University's CCV OSCAR: De-identified data (including DICOMS, cognitive testing data, and exported REDCap data) will be transferred to Brown University's CCV OSCAR (Ocean State Center for Advanced Resources) for advanced analyses. Please view Appendix A for more details.

F9. Data security plan

All study information will only be accessible by study staff included in the IRB-approved study protocol.

F9.1 Paperwork: Paper documents containing de-personalized data will be stored in building 32 (doubled locked building) in a locked file cabinet in the PI's office, or in a locked cabinet accessible by only study staff in room 143. Phone screening questionnaires, HIPAA authorizations, informed consent forms, and demographic forms, will be stored in a locked cabinet separate from study data files in the PI's lockable office.

F9.2 Electronic data and audio-recordings: All VA sensitive information containing PHI (contact information, subject identification logs, audio-recordings) will be stored on a secure VA server location in a restricted folder e.g. \\R04pronas21\RESEARCH_PROTOCOLS\Philip\MRI_TMS+BCBT-R, unless otherwise indicated (e.g. HIPAA, informed consent paperwork). These computer files are protected from unauthorized access by IRM-assigned permissions.

granted to study staff. Identifiable contact information collected during the prescreening process will be recorded in an electronic password-protected recruitment log. Links to subject identification codes will be stored in a password-protected Excel log file. Logs with identification codes will not be stored in the same subfolder as the main research database. Audio-recordings collected during Visit 1 will be uploaded immediately at the end of the session and will be deleted from hand-held recorders after upload.

F9.3 MRI**:** CD/DVDs (raw, de-identified MRI data) will be stored in building 32. Following the transfer of data from the PVAMC scanner to the encrypted hard drive, the data will be stored for back-up on the secure research server. A back-up copy will be made onto a CD/DVD and stored in a locked cabinet the PI's office. Another copy will also be transferred to the Apple Super Computer for analysis.

F10. Data on hard drives

F10.1 Cognitive tasks**:** Data obtained from cognitive tasks on either the password protected Apple laptop or iPad will be temporarily stored on the device hard drive prior to transfer to the Aegis Fortress L3 encrypted hard drive. Data will be deleted from the laptop after successful transfer to the secured research server (\\ r04pronas21.v01.med.va.gov\RESEARCH_PROTOCOLS\Philip\MRI_TMS+BCBT-R).
Study staff will assure that this information is deleted by emptying the trash bin after deleting the information.

F10.2 MRI data: An Aegis Fortress L3 encrypted hard drive will be used to transfer MRI data from the MRI acquisition computer to the VA research server and to Apple Super Computers. This encrypted drive is VA FIPS-140-2 validated and requires and pins to unlock. See attached SOP for more details. De-identified MRI data currently under analysis will be stored on VA Research- owned, password-protected, non-encrypted Apple Super Computers with removable large- capacity external solid state hard drives/file servers. The workstation is in the double-locked research Building 32, room 149. The Apple Super Computer and drive are not connected to the VA network. The hard drives are not encrypted due to data access/read-write speed requirements.

F11. Mobile devices
Mobile devices used in this study are a VA-approved audio recorder (Phillips Digital Voice Recorder DPM-8000), Apple laptop, iPad, and Aegis Fortress L3 encrypted drive. These devices are not on the VA network and will have wireless or 802.11 connectivity disabled (laptop and iPad). Identifiable information will not be entered into iPads or laptops. Laptop and iPads are un-encrypted, because encryption prevents these devices from interacting properly with the MRI scanner during data collection. The hard drive is encrypted – see attached SOP for more information.

F12. Removal of sensitive VA data from the protected VA environment

No identifiable information will be shared outside the Providence VAMC.

F13. Protection of media stored at an alternate site

The principle investigator may share de-identified final datasets, statistics, and results by depositing these data at the National Library of Medicine (NLM) PubMed Central website repository. This is a VA-supported data repository.

Additional documentation including metadata such as information about data collection, analysis code, and definitions of variables may also be shared. Scientists and the public benefit from data sharing because it incentivizes scientists to uphold best research and data management practices. Data sharing also promotes independent replication of results by external research groups. Sharing also promotes collaboration amongst researchers which is especially important when conducting research on low base rate behaviors such as suicide.

F14. Data transmission

No sensitive electronic data are transferred in this study. Anonymous information may be shared with the research staff electronically for the purpose of study discussion and analysis.

F15. Data backup

Original VA research data saved on the VA network will be backed up regularly and stored securely within the VA's protected environment. . The MRI data is duplicated on DVD/CDs and backed-up on the VA research server. Secondary imaging files created during analyses conducted on non-networked workstations will be backed up on partitioned large-capacity external hard drive/file serves stored in Bldg. 32, room 149. Partitioning enables redundant backup of imaging data. The size of the completed final analysis may be ~8 terabytes. This is estimated based on 1 TB size of a recently completed imaging analysis that used a lesser amount of imaging data. Weekly scheduled backups of non-networked computers will be managed by the PI.

F16. Shipping data

No data are shipped in this study.

F17. Data destruction

Records will be maintained in accordance with the Department of Veterans Affairs Record Control Schedule 10-1: it will be destroyed 6 years after the end of the fiscal year of the IRB closure of this study.

F18. Termination of data access

The PI will be responsible for assuring that VA access accounts are terminated when a user no longer needs access.

F19. Incident reporting

If theft, loss, unauthorized access of sensitive data or storage devices, or non-compliance with security controls occurs, the Information Security Officer (ISO) will be notified immediately. Research staff will carry out any necessary procedures given by the ISO to resolve the situation**.**

Figure 3. Devices and technology flow

G. HUMAN SUBJECTS PROCEDURES

G1. Sources of Material

Data collection will be conducted in accordance with HIPAA guidelines and PVAMC IRB- approved protocol. Potential Veteran subjects with STBs will be recruited from either the inpatient psychiatric unit at PVAMC or through clinician or Suicide Prevention Coordinator referrals. If the patient appears appropriate, the study will be explained to the patient's treating physician. If the attending physician agrees to the patient's participation, a member of the research team will then approach the patient. The nature, purpose, and risks and benefits of the study will be explained to the patient and informed consent will be obtained.

Data collected for this project will be used for research purposes only. Separate locked, secure files will be used to store study materials for each participant. An identity masking subject number will be assigned to each participant. Collected information will be identified by subject number only. A list linking the names of the participants with their subject numbers will be kept in a secure, password-protected computer account accessible only to the Principal Investigator(s).

De-identified data (e.g. questionnaires, self-report measures, imaging data, cognitive task data, scores from interviews),with the exception of assessment dates, from this project may be shared with PVAMC protocol #2018-051 entitled “Neuroimaging of a Suicidal Thoughts and Behaviors,” led by investigator Dr. Jennifer Barredo and PVAMC protocol #IRB-2020-008 entitled “Longitudinal Assessment of the Sleep- Suicide Link in Veterans Discharged from Inpatient Psychiatric Care,” led by investigators Dr.
Jennifer Primack and Dr. John McGeary. De-identified interview data, with the exception of assessment dates, from this study may also be shared with the PVAMC protocol “Longitudinal Assessment of the Sleep-Suicide Link in Veterans Discharged from Inpatient Psychiatric Care” (IRB-2020-008) led by investigators Dr. Jennifer Primack and Dr. John McGeary. These interview recordings would be shared for training purposes. Only approved members of the study will have access to recordings containing identifiable data.

Five sources of data will be included in this project. These include: 1) the initial screens,
2) questionnaires, 3) structured and semi-structured interviews, 4) MRI data, and 5) electronic health record data obtained from participants CPRS files.

G1.1. Screens: Each potential participant will be interviewed by research staff to determine initial study eligibility. All information from this screen will be identified with subject numbers only.

G1.2. Questionnaires: Self-report measures will be administered at during the initial testing session. This information will be identified with subject numbers only. Paper copies of data collected will be stored in a locked filing cabinet in PVAMC bldg. 32, rm.

143. Responses from assessments will be entered into VA REDCap and identified only by subject number.

G1.3. Structured and semi-structured interviews: These interviews will be audio- recorded. Recordings will be immediately uploaded to a restricted VA server and identified by participant number only. Recordings will be deleted from tape recorders

immediately upon uploading to the server. Tape recorders will be kept in a locked filing cabinet in the offices of the principal investigator(s) or research assistants. All information on paper obtained from these interviews will be identified with subject numbers only and will be kept in a locked filing cabinet behind keycard-secured doors in PVAMC building 32. Electronic records of responses made during interviews will be entered into VA REDCap. Data in REDCap is only identified by subject number.

G1.4. MRI data: All MRI data will be collected using subject numbers only and will be recorded

G1.5. Electronic health record data: All information obtained from patients CPRS files will be identified with subject numbers only and will be recorded in VA REDCap.

G2. Potential Risks and Protections for Subjects

G2.1 Informed Consent: Administration of informed consent procedures will be performed under conditions approved by the PVAMC IRB. Informed consent will be obtained in-person by trained study staff familiar with both the study and with MRI methodology. Prior to consent, subjects will be informed of their rights as a research subject, warned about any known risks or benefits of the methodology, and will be informed of study procedures. Research personnel will review all parts of the consent form with participants, including the assessments and protocol, limits to confidentiality, alternatives to participation, as well as the right to withdraw from the study without penalty.

All potential participants will be asked to read and complete an informed consent after going through the form in detail with a member of the research staff. Research staff will be available to answer questions and ensure that the participant understands the form. Research personnel will review all parts of the consent form with participants, including the description of study assessments and protocol, limits to confidentiality, alternatives to participation, and potential risks and benefits, as well as the right to withdraw from the study without penalty.

If a participant withdraws (officially or unofficially) at any time from the study, the study investigator will follow-up with the participants mental health provider notifying them of discontinuation in the study following good clinical practice procedures.

Participants will be informed that their involvement in this study, or refusal to participate, will not affect their treatment with the VA. Participants will be given contact numbers for PIs and for the IRB (including afterhours contact information). The PIs will be available to answer any questions or provide additional information.
Participants may be asked to sign releases of information to non-VA providers to gather additional information for this study. Consent will be documented on an IRB approved form.

G2.2 Coercion: Though it will be emphasized during recruitment and the informed consent procedure that participation is voluntary and

may be terminated by the participant at any time, there is a possibility that Veterans may feel coerced into participating.

The risk of potential coercion will be minimized by following standard procedures for obtaining informed consent. We will fully explain the study procedures, risks, benefits and alternatives to all patients and significant others. Also, patients who do not consent or who withdraw at any time will receive usual clinical treatment with no

prejudice. Although compensation for participation is provided, we do not believe that the total compensation amount (as noted in in the Study Procedures) is excessive or coercive.

G2.3 Confidentiality: There is some risk to patient confidentiality associated with participation in research clinical trials, as more data are collected than would happen in usual medical practice. Steps will be taken to protect privacy of patient health information. Patients will be told that information about their TMS treatment may be shared with their prescribing mental health provider and/or primary care provider, per best-practice standards. Every effort to maintain participant confidentiality will be made.

All interviews will be conducted at the Providence VAMC research building and all hard copy data will be maintained on hospital grounds. Audio files of the sessions will be immediately uploaded to a VA secure, restricted server. Participants' records/assessments will not become a part of their permanent medical record. Study forms and data will be identified by code numbers only, and will be stored in locked file cabinets or on VA-owned computing resources. Identifying information (contact information, name, consent documents) will be stored separately from research data in a dedicated locked file cabinet or in a password-protected Excel file in a dedicated restricted folder on the secured VA-research server. Personal participant information will not be presented in publications or presentations resulting from this research. Only the PIs and study staff will have access to study materials. The Principal Investigators are responsible for ensuring that study personnel are trained in the responsible conduct of research.

In exceptional circumstances, confidentiality may be compromised. These circumstances include mandatory reporting requirements for the State of Rhode Island for child and elder abuse and in situations in which the risk of suicide or homicide is imminent. Patients will be informed of these potential risks to confidentiality during the informed consent process.

G2.4 Inconvenience and Burden of Time/Travel: Subjects may engage in screening procedures and learn they are not eligible for participation in the research treatment trial. Emotional discomfort may be associated with completing the assessments and questionnaires. Frequent visits to the research clinic for the TMS treatments may represent an inconvenience, especially if a subject must travel a great distance or has other constraints on their time or transportation. A small payment will be offered (*see Study Procedures for details*) to cover part of the subject's expenses related to participation in this research study, but subjects will not be offered reimbursement for all the expenses they may incur.

G2.5 Risks of Assessments: There is a risk of discomfort when being asked to rate clinical symptoms or disclose information about suicidal thoughts and behaviors. Subjects will be informed that if they experience discomfort during symptom assessment, study personnel will take appropriate measures, including debriefing and referral to the principal investigators for further evaluation.

G2.6 Procedures for Handling Suicidality: The potential for adverse events is possible during the study, including suicidal ideation or behavior or other adverse events and will be minimized by the following procedures:

1. If the patient's psychotherapy is focused on suicide or overlaps significant with BCBT for suicide, patients may be asked to refrain from this suicide-for individual psychotherapy for the active treatment phase of the project (3 months). We will discuss this temporary change before enrollment with the treating therapist to ensure that it is clinically appropriate with the understanding that the patient may return to his/her usual psychotherapy after receiving study treatment. However, all subjects will continue to receive their pharmacotherapy as usual during the study. Thus, adverse events will be minimized by continued medication treatment and increased clinical monitoring as part of study procedures/assessments in both intervention conditions.
2. All subjects in the study will receive enhanced monitoring of their clinical condition. BCBT therapists will routinely monitor levels of suicidal ideation and risk, as well as overall psychiatric symptoms, and take appropriate clinical action when necessary to reduce risk. In addition, all participants will be monitored closely and assessed at posttreatment follow-up sessions (*see C3. Data Collection*).
3. We will have procedures in place to respond to clinical deterioration. If a safety risk or deterioration is identified, we will inform the treatment team and provide emergency or referral services as needed.
4. If any patient reports suicidal ideation or behavior, this will be assessed and appropriate measures will be taken as noted in previous sections.

Regarding imminent self- or other-harm, there is a specific protocol within the Providence VA Medical Center System for handling behavioral crises, which is contingent upon whether the person(s) is on-site or off-site when such emergencies arise. On site, we have "Team 3" buttons for each clinician or research assistant that are directly linked to the Providence VA Medical Center police department and additionally request a team of mental health workers trained in crisis management. If there is imminent risk to self or another, we will collaborate with Providence VA Medical Center's staff in Interim Care to triage the patient to receive the appropriate emergency services. If a participant is at imminent risk, the PI or trained study staff will escort the participant to Interim Care or Emergency Services at the Providence VA Medical Center. The clinical staff there will evaluate the need for emergency services, and triage the patient to receive the appropriate services. We will also provide a list of crisis hotline numbers and community resources that participants may access, for example, the Department of Veterans Affairs suicide prevention hotline number (800-273-TALK).

Relevant to risk for harm to self or others and suspected abuse or neglect of vulnerable persons (see below), participants are informed in the Informed Consent Procedures that these are circumstances in which confidentiality is not protected. In addition, if a participant must be terminated from the protocol due to safety concerns, if there is no referring

clinician and there is the need for referral, we will provide referral resources for the participant.

G2.7 Risks Related to Intervention:

G2.7.1 Side effects of TMS treatments:

During treatments, patients may experience a sensation of tapping or painful sensations around the place where the treatment coil is positioned on the head. Most patients who have had TMS therapy usually report these sensations to be mild and find it diminishes over time as their body adjusts to the daily treatment procedure.

Other possible side effects associated with TMS delivered to this standard target on the head are scalp, jaw, face, or neck discomfort or muscle twitching in those area, toothache, and headache. When TMS has been delivered to areas of the brain outside of the target location where the coil is placed in this study, there have been reports of transient dizziness, fainting, and brief changes in attention and thinking. These are considered extremely rare and highly unlikely to occur in subjects as planned in this study. The device also emits a loud clicking noise that can potentially lead to hearing problems.

Some treatment coil adjustments may be possible to make the experience more comfortable. Over-the-counter pain medications such as acetaminophen or ibuprofen are helpful for reducing discomfort from TMS treatments. Assessment of the subjects' well- being and functioning before and after each treatment, special positioning and targeting procedures to ensure the coil is placed over the specific brain region in this study, and constant monitoring during each treatment session, will all be done to minimize the risk of experiencing side effects. Because the device can emit a loud clicking noise during treatments, all subjects will wear protective earplugs or occlusive ear buds during TMS.

G2.7.2 Seizure from TMS:

It is estimated that in ordinary clinical use, standard clinical TMS treatments have caused a seizure in approximately 0.1% of patients, representing a risk of seizure in approximately 1 in 30,000 treatments. The TMS treatments in this study will be administered by staff personnel who have extensive experience with safe delivery of brain stimulation and who are trained in steps to prevent and manage seizures.

Medical personnel and equipment are available at PVAMC to monitor subjects and apply appropriate medical procedures if a seizure occurs. Most seizures last only a few minutes and spontaneously end, with the patient in a somewhat confused state that resolves over several hours. Management of a seizure during TMS may involve transferring patients to the emergency room for further evaluation, if that is determined to be necessary by the study doctor. Should a subject experience a seizure that is related to TMS in this research, a doctor will provide them with a letter stating that the seizure was produced under specific brain stimulation conditions in this study, and that there is no reason to expect another seizure would occur when not receiving TMS.

Furthermore, a licensed study physician with experience and TMS training will determine the motor threshold and deliver, or supervise delivery, of the TMS pulses. This physician will be available throughout all TMS sessions, and a qualified technician will be present during all TMS sessions. Side effects of TMS will be used to identify and address any TMS-emergent adverse effects following best clinical practices. Risk of seizure and other serious adverse events related to stimulation will be mitigated by careful screening of past health history, identification of underlying risk factors, application of the study inclusion/exclusion criteria and use of chosen stimulation parameters. Risk of discomfort from stimulation will be addressed through pre-TMS assessment of tolerability and potential reduction of the intensity of delivered pulses.

G2.7.3 Worsening Symptoms or Lack of Improvement:

There is a potential lack of positive response to BCBT or TMS, worsening of psychiatric symptoms, and no guarantee that the treatment will lead to improvement of symptoms. Suicidality may increase if symptoms do not improve. All participants will be receiving VA treatment as usual. If our staff identify an individual with significant clinical deterioration or who report any suicidal ideation with plan or intent they will contact one of the designated VA research study Psychiatrists who will evaluate the patient over the phone or in person. A list of m

be available in case of emergency. If a study participant reports significant deterioration but is not in immediate danger of hurting himself, we will take the following actions. First, we will inform patients about the procedures for contacting emergency services should they find themselves at risk for self-harm. Second, we will contact their outpatient psychiatrist or other primary clinician to inform them of their deterioration. Third, if there is an increase in suicidality during any TMS sessions, the TMS provider will immediately alert the designated study clinical

coverage personnel. In any event that a participant is acutely suicidal, the research staff member will walk the Veteran over to Interim Care or the ER for immediate safety assessment. All serious adverse events will be immediately recorded and reported to the Providence VAMC IRB and DSMB according to policy.

G2.8 Risks Related to Neuroimaging: There are no known physical, psychological, social, legal or other risks associated with participation in MRI at the level of magnetic field proposed here beyond those posed by the existence of an implanted non-MR safe metal device or metal fragment, or of claustrophobia. Multiple screens for contraindications are administered to eliminate significant risk. On rare occasions, subjects have reported heating of tattoos in the MRI. Participants with tattoos will be monitored for heating while in the MRI scanner.

The PI or trained study staff will discuss MRI visit procedures, including safety measures, in detail with the participant at the end of the baseline visit. Safety information is also included in the Informed Consent materials. They will be informed that there is a risk of claustrophobia during the scan; investigators and research technicians trained in screening procedures will evaluate for claustrophobia and take appropriate measures, including referrals to treatment. Subjects will be informed of the risk of heating from radiofrequency coils and instructed to inform the research technicians if this occurs. Subjects will also be informed that the scan session provided does not constitute a clinical scan and that researchers are not board- certified radiologists. If there is concern for a physical abnormality on structural scan, the PI will provide an appropriate referral. All serious treatment- emergent adverse events will be brought to the VA IRB as required in IRB protocols.

G2.8.1 MRI safety training of study staff Study staff involved in Visit 2 sessions will have completed at a minimum Level 1 MRI safety training through the VA Talent Management System (TMS). Training involves viewing of safety videos, reviews of safety white papers, and one-on-one training with MRI facility operators or managers. Before scanning staff must demonstrate knowledge of:

- Subject preparation procedures (clothing, securing valuables, execution of screening form, explanation of MRI exam).
- MRI scan room and equipment (door overrides, table controls, intercom, emergency squeeze ball, linen, storage and use of RF coils)
- Emergency procedures for medical emergencies e.g. cardiac arrest.
- Emergency procedures for situations presenting an immediate threat to human life or to the facility infrastructure i.e. procedures for Siemens quench and emergency run-down and subject evacuation during an adverse event.

G2.8.2 MRI-contraindication screening. Potential participants CPRS files will be reviewed for potential MRI contraindications by the PI or study staff during pre- screeni

undergo screening for MRI contraindications, metal implants, or the possibility of accidental lodging of metal fragments three times: 1) by the PI or study staff conducting the enrollment screening, 2) by the PI or study staff at the MRI facility outside of the scanner room during Visit 2, and 3) by the MRI technician just prior to entering the scanner room.

G2.8.3 Participant safety and comfort monitoring. MRI operators and study staff will monitor participants using 2-way voice intercom, infrared camera, and psychophysiologic data (i.e., pulse and respiration rate). Prior to scanning, participants will be trained to use a squeeze bulb alarm system that will immediately signal distress to the scanner operator. One co-Principle Investigators is a Board-

Certified Psychiatrist (Noah S. Philip, MD) and can be available to assess clinical needs and make referrals if acute management is needed.

G3. Potential Benefits of the Research to Subjects and Others

The potential benefits of identifying effective treatments for suicidal patients appear to outweigh the potential risks of this study. Both BCBT and TMS alone have been found to reduce suicidal ideation and we believe that participants in both conditions will experience significant improvement in symptoms. Improvements in assessment and treatment of suicidal patients are urgently needed. The major risk, that of adverse events, should not be increased by study participation and in fact should be reduced by the enhanced monitoring and risk reduction procedures noted above. If neuroimaging biomarkers are clinically useful, participants may gain access to related technology that may help them self-monitor their suicidal risk at a later date.

Any incidental neurological information gained during scanning of the brain may be of potential benefit to subject and the subject's physician.

G4. Importance of the Knowledge to be Gained

Suicidal behavior is a significant public health issue and of critical importance to Veterans. The evaluation of interventions to reduce suicidal behavior may have important benefits for multiple aspects of society. Additionally, this study will advance our understanding of the neurobiology of suicidality. These findings can be used to develop neurobiology-based clinical criteria for identifying Veterans at elevated risk for suicide. Importantly, these objective measures are less susceptible to the reliability issues that affect the accuracy of self-report measures. Knowledge gained will be fundamental for the development of targeted therapeutic interventions that can modulate neural function in regions implicated in suicide. Thus, our results will have important implications for a variety of stakeholders, including patients, family members, healthcare providers, managed care organizations, health insurers, administrators, and policy makers.

G5. Data and Safety Monitoring Plan

Weekly meetings with study staff and study investigators will be held to review progress with regard to enrollment, any adverse events, and attrition/noncompliance. Circumstances surrounding any identified adverse events, incidents of subject dissatisfaction, or subject noncompliance/withdrawal of consent will be tracked regularly and discussed. Adverse events tracking files will be routinely updated. If data patterns consistent with any safety issues are suggested, the principal investigator will seek consultation with, and peer review by, other

experienced research colleagues who have executed similar studies with the methods and procedures of concern.

Serious adverse events will be identified and promptly reported to the Providence VA IRB as required. A member of the research team will be on-site during all

sessions, and in the event of any subject becoming unstable or demonstrating clinical symptoms, the principal investigator and/or study team will assess the subject and facilitate subsequent treatment or referral. All research and staff members are trained in

basic first aid, CPR, and appropriate MRI, and brain stimulation safety/evacuation protocols. All members of the research team have 24-hour access to investigators or covering psychiatrists on site for management of any clinical emergency that may arise. To ensure the integrity of the data the PI and study team will review all the data for errors or inaccuracy within one week after it is obtained. All data will be entered into a research database as it is collected (i.e. RedCAP), and the research assistant will meet with PI weekly or as appropriate to review ongoing subject data.

G6. Inclusion of Women, Minorities and Children

This proposal acknowledges, and will adhere to, VA policy to include women, minorities and children in research. The gender and minority balance of the Providence VAMC reflects the broader demographic of Veterans and local demographic distribution of Providence, Rhode Island. Pursuant to VA policy, people below the age of 18 will not be included in this research. Veterans below the age of 21, but above the age of 18 will not be excluded when they meet eligibility for the study and sign informed consent. The number of participants that are between 18 and 21 years of age is anticipated to be limited since this age range is not broadly represented in patients receiving care at the Providence VA.

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