Personalized Therapeutic Neuromodulation for Anhedonic Depression

Study Protocol and Statistical Analysis Plan

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Study Protocol Title: Personalized Therapeutic Neuromodulation for Anhedonic Depression
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Research Synopsis

The primary goals of this project are to identify novel neurobiological subtypes of anhedonic depression that are expected to respond differently to treatment; to develop brain-behavior biomarkers for diagnosing those subtypes in individual subjects, relying on inexpensive behavioral and clinical measures in most cases; and to build an analytic pipeline for rapidly identifying who needs rTMS and determining the optimal individualized stimulation protocol and dosing regimen. Our approach will evaluate predictive validity in held-out samples, and our models will incorporate multiple levels of analysis, including network connectivity, plasticity, behavioral and self-report measures of reward processing, and treatment outcomes. The end result will be a comprehensive model to match pharmacological and rTMS treatments to individual patient biology within days of their first encounter with a psychiatrist—precision medicine for anhedonia, eliminating the need for trial-and-error in treatment.

Background and Significance

As reviewed in detail above, depression is highly prevalent and disabling(1), and SSRIs, psychotherapy, and other first-line treatments are simply not effective in many patients(2). New approaches are urgently needed, especially for anhedonic depression, which is often especially resistant to conventional antidepressants(3–5). rTMS is a promising and potentially transformative alternative to SSRI antidepressants and other first-line treatments(6,7). Recent work from our labs and others indicate that there is significant potential for enhancing existing rTMS protocols to rapidly achieve markedly improved treatment outcomes. Our project is designed to address three key challenges to achieving this goal: 1) parsing heterogeneity in anhedonic depression for the purpose of treatment matching; 2) individually tailoring rTMS protocols to achieve better outcomes; and 3) identifying the optimal rTMS dose and target site. Below, we review these challenges and potential solutions.

Parsing heterogeneity in anhedonic depression. Depression is not a unitary disease entity; it is a syndrome that is diagnosed when a patient presents with five or more of nine symptoms, meaning there are at least 256 unique symptom combinations meeting criteria for this diagnosis. Depression subtypes defined by distinct biological mechanisms and potentially requiring different treatments are widely assumed to exist, but there is no consensus on how to define them. Pioneering efforts to parse heterogeneity in depression have defined subtypes characterized by symptoms that tend to co-occur in subsets of patients (e.g. atypical, melancholic, and seasonal

depression), and then examined whether they are associated with potential biomarkers. Our team has developed and validated a converse approach, subgrouping patients based on biological measures and then testing whether the resulting subtypes are associated with distinct clinical symptom profiles and treatment outcomes. In our initial efforts(8), we identified two brain-behavior dimensions predicting individual differences in anhedonia and anxiety. Hierarchical clustering revealed four subtypes associated with distinct clinical symptom profiles, differing patterns of connectivity in frontostriatal, limbic, and thalamic networks, as indexed by rsfMRI, and differing DMPFC- rTMS response rates.

One limitation of this work is that the retrospective samples analyzed in our prior studies were not designed to study anhedonia specifically. Thus, in this project, we will apply the methodology we have developed over the past five years to focus specifically on anhedonia (including numerous technical advances described below), with the goal of discovering novel subtypes of anhedonic depression and defining brain-behavior biomarkers for diagnosing them in individual patients (Aim 1). This in turn, will enable efforts in Aims 2–3 to develop individualized treatment matching algorithms that will determine who requires rTMS (i.e. predicting SSRI non-responders) and identifying the optimal individualized stimulation protocol, target site, and dosing regimen.

Individualizing Theta Burst Stimulation (TBS) to Maximize Plasticity. A second opportunity for achieving better rTMS outcomes is that we do not yet know how to tailor the stimulation protocol for individual patients. TBS is a relatively new form of TMS where pulses are applied in very short bursts (three pulses at a time) but at high frequencies (usually around 50 Hz). These short bursts are repeated at an inter-burst interval of 200 milliseconds (ms). TBS was initially developed as a stimulation method designed to mimic the endogenous theta rhythm of the brain found on electroencephalogram (EEG). TBS as a therapeutic modality is based on the notion that modulating theta activity alters gamma activity, which is critical for neocortex-mediated cognitive functions(9). In animal models, stimulation with TBS-like protocols has been shown to alter brain synaptic plasticity in a sustained manner, by means of long-term potentiation (LTP) and long-term depression (LTD)(10).
Two types of TBS have been studied to date: 1) intermittent TBS (iTBS) – brief stimulation trains followed by a period of rest, e.g., 2 seconds of stimulation followed by 8 seconds of rest; and 2) continuous TBS (cTBS) – brief stimulation trains continuously, e.g. trains of stimulation bursts are administered continuously for 20-40 seconds. On fMRI studies, iTBS and cTBS exert opposite effects on brain activity: iTBS consistently produces an increase in local cortical excitability (i.e., neuroplasticity), while cTBS produces a decrease in excitability(9). Similar effects have been seen in studies on motor cortical excitability and excitability of prefrontal brain regions using combined TMS-EEG methods(11). Of note, iTBS effects appear to persist for at least as long, if not longer, than the effects produced by standard rTMS protocols, despite taking only a fraction of time(9).

TBS appears to be as effective as standard TMS in the treatment of depression. A series of small open-label and randomized controlled trials (RCTs) provided preliminary evidence for the antidepressant efficacy of TBS approaches, most substantially iTBS applied to the left dorsolateral prefrontal cortex (DLPFC) or sequential bilateral stimulation combining left-sided iTBS and right-sided cTBS(12,13). The most definitive evidence for the antidepressant efficacy of

TBS, however, comes from the large, multi-site non-inferiority THREE-D trial (co- led by MPI Daskalakis), showing that iTBS was non-inferior to standard 10Hz rTMS in relation to antidepressant efficacy in TRD when both stimulation protocols were applied to the left prefrontal cortex(7). In a recent review, iTBS was also well tolerated and not associated with adverse effects(14).

Optimizing theta-burst stimulation to improve clinical outcomes. Here, we will test a highly promising method to improve outcomes by individualizing burst stimulation frequency during the application of iTBS to produce substantially greater neurophysiological changes. rTMS is thought to exert its antidepressant effects partly by entraining endogenous oscillations at the frequency of stimulation. rTMS treatment is typically delivered at a fixed stimulation frequency—most commonly 10 Hz on the left or 1 Hz on the right. In Aim 2, we will test whether improved clinical outcomes can be achieved by stimulating at a frequency that is specific to an individual, e.g., at an individual subject's peak alpha frequency (i.e., between 8-12 Hz) rather than a fixed 10 Hz. Individualization of treatment frequency has the potential to reset activity in cortical-subcortical oscillatory networks. Given that entrainment is much more efficient when an external stimulus is applied close to an individual patient's endogenous rhythm(15,16), individualization of stimulation frequency is likely to enhance coupling of exogenously applied and endogenous brain rhythms. As described in more detail below, we have developed a new method to individualize the burst frequency in iTBS using the concept of theta-gamma coupling. Our preliminary data highlight the potential of this approach for improving treatment outcomes.

Optimizing Dosing: Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT). We have developed and validated a novel accelerated iTBS approach, which we termed SAINT (Stanford Accelerated Intelligent Neuromodulation Therapy). Conventional rTMS exerts its antidepressant effect after a 6-week (90,000-pulse) course of treatment, with remission rates remaining relatively low at around ≦ 30%.24 Our SAINT approach, by contrast, has been shown to induce rapid remission (in 1-5 days) at high rates (>90%) in patients with severe treatment resistant depression (TRD) with no evidence of cognitive side-effects(17). This approach combines (1) iTBS stimulation parameters(12), (2) an accelerated/patterned schedule(18), and (3) a novel, personalized targeting approach(19,20), which all appear to contribute to this approach's ability to rapidly produce sustained reductions in depressive symptoms, including anhedonia. This approach is the most aggressive rTMS protocol published to date, in which an entire course of rTMS (18,000 pulses)(7) can be applied each day(17,21). At present, the dose-response curve of theta burst stimulation for anhedonia is unknown. It is possible that relief from anhedonia could be achieved with less time and stimulation than our standard SAINT method calls for. In order to determine the minimally effective dose, we will use a daily assessment battery to identify in a temporally granular fashion at what point in time relief from anhedonia begins to appear.

SAINT is highly effective for Treatment Resistant Depression. In our recently completed SAINT RCT we randomized 32 participants with TRD (Maudsley Staging Method score ≥7) and treated 29 participants. We observed a high rate of remission, with 86% of participants

experiencing remission at some point during the 4 week follow up period in the active group (12/14, MADRS≤10) versus a low rate of remission in the sham group (13%; 2/15). We found an average reduction of 66% in depression symptoms (MADRS) immediately after SAINT in the active group vs. 6% in the sham group. 10/14 participants showed a ≥50% reduction in symptoms in active versus 2/15 in sham, and 8/14 (57%) remitting from depression after 5 days of SAINT in active versus 0/15 in sham, despite having failed numerous treatments(22). By comparison, after an acute course of open-label ECT, there is an average of a 48% remission rate for individuals with TRD(23). We followed our participants for 4 weeks, observing a median 65-82% reduction in the MADRS. At one-month post-SAINT, 64% of active-group participants continued to be responders, and 43% were in full remission. Mean MADRS scores remained significantly lower than baseline.

Optimizing Target Selection for SAINT in the treatment of anhedonia. Although several cortical and subcortical targets have proven to be effective for the relief of anhedonic symptoms through invasive and noninvasive neuromodulation, there is good reason to believe that the subgenual anterior cingulate cortex (sgACC), the left dorsolateral prefrontal cortex (L-DLPFC), and the dorsomedial prefrontal cortex (DMPFC), are likely to be efficacious targets for the reduction of anhedonia, based on prior human and animal work. The sgACC's role in anhedonia is supported by primate studies wherein stimulation of its subregions resulted in distinct patterns of anhedonic symptoms(24), and in rodent studies in which researchers were able to reduce anhedonia-like symptoms (as measured by the forced swim test and sucrose preference) by stimulating the rat vmPFC(25). In humans, DBS stimulation of the sgACC has shown promise for the relief of treatment-resistant depression(26–28). In addition, our own RCT, in which the sgACC was targeted noninvasively (by targeting cortical locations that were anticorrelated with it)(22) produced strong anti-hedonic effects (see above). Other candidate subcortical targets we considered include the nucleus accumbens(29) and medial forebrain bundle(30), but we chose the sgACC primarily on the basis of our prior results(17,22).

Two cortical targets that are functionally connected with the sgACC have shown promise for the treatment of anhedonia. Theta burst stimulation applied to the DMPFC selectively reduced anhedonic symptoms in a depressed patient population(31). Reward network connectivity appears to play a role in determining the effectiveness of this target for depression(5), suggesting it may be a good candidate target for the identification of patient-specific biotypes. TMS applied to the left DLPFC has been shown in a number of studies to reduce symptoms of anhedonia(17,22,32,33), and as with DMPFC, reward network connectivity may mediate the effectiveness of this target(34). We have developed a method for identifying cortical locations that are maximally anticorrelated with metabolic activity in the sgACC, enabling us to simultaneously modify activity in cortical targets and in the sgACC. By identifying distinct biotypes of anhedonia, we will determine whether the benefit individuals derive from a L-DLPFC/sgACC target, or a DMPFC/sgACC target, depends on their anhedonic biotype.

Individualization of iTBS by personalizing frequency of burst stimulation. As discussed above, we will also test a highly promising method to improve anhedonia outcomes by individualizing theta burst stimulation frequency to produce substantially greater neurophysiological changes. To this end, we have developed a new method to individualize the burst frequency in iTBS using the concept of theta-gamma coupling (TGC). This method allows for individualization of both theta and gamma frequencies during the application of a TBS paradigm. TGC refers to the dynamic interaction between theta and gamma frequencies(35) often seen during the performance of working memory tasks and is believed to be essential to the function of working memory(35,36). A series of studies from our group identified a significant relationship between TGC and depression. We found that there is an increase in TGC produced with rTMS in depression, and this increase in TGC is associated with an increase in hippocampal volume and in aspects of improved cognitive performance(37,38). Moreover, with deep brain stimulation, we also found an increase in TGC, which was correlated with a reduction in depressive symptoms(39). Our novel approach involves the assessment of TGC during a working memory (3-back) task, which elicits consistent TGC and is abnormal in patients with depression(40). From this task, theta and gamma frequencies are determined to then individualize the iTBS stimulation regime (11). A detailed description of the method of assessment of TGC is provided in(11), which also confirmed the stability of the TGC assessment.
In a principle study, we applied single trains of frequency-individualized iTBS were applied to the PFC in healthy volunteers and compared the effects to iTBS applied using two standard fixed protocols: 6/30Hz and 5/50Hz. Neuroplasticity was indexed using combined TMS-EEG and on both mood (using a standard visual-analogue scale assessment previously used in healthy subjects) and working memory performance(11).
Frequency-individualized iTBS produced: 1) improved mood that was only seen in the frequency individualized iTBS group; 2) increased neuroplasticity, as evidenced through a significant increase in cortical evoked potentials through TMS-EEG (i.e., increased P60, N100 and P200 TMS evoked potentials); and 3) improved working memory accuracy. Additionally, improved mood in the frequency-individualized iTBS group was correlated with increased plasticity.

We will pursue two approaches to the individualization of iTBS treatment of anhedonic depression. First, we have developed an approach to individualize the frequency at which TBS is delivered. Individualization of TBS frequency (Ind-iTBS) is based upon the assessment of theta-gamma phase coupling (TGC) in an individual patient during a working memory task. Second, we have developed a method to also individualize the targeting of stimulation sites for TBS by using neuroimaging-guided targeting and E-field modeling to ensure optimal cortical localization over the DLPFC. Third, we have developed novel methods to evaluate neuroplasticity directly from the DLPFC. Through combined TMS with EEG, we can ascertain changes in cortical evoked potentials elicited through treatment with iTBS that represents a neurophysiological index of neuroplasticity directly from the DLPFC(41).

Individualization of iTBS by cortical e-field targeting. To further optimize and individualize the iTBS stimulation protocol, we will model the TMS electric field (E-field) to better target the desired area of DLPFC (see below for functional targeting details). E-field modeling is used to optimize coil placement and engagement with the desired cortical target by accounting for anatomic

variability and maximizing dosing. This is motivated by the fact that the head anatomy varies considerably between subjects and this variability results in significant differences in the distance from the TMS coil to the cortex(42). Moreover, differences in the gyral shape and orientation, coupled with transitions in electrical conductivity between the CSF, grey matter and white matter, significantly alter the current distribution produced by a TMS pulse in a manner that is dependent on coil orientation(43). Finally, the e-field direction relative to the cortical columns affects the degree to which neurons are activated(44). Traditional methods of dosing rTMS in depression titrate intensity based upon stimulation of the motor cortex (i.e., the resting motor threshold) and situate the coil oriented 45° to the sagittal plane in all subjects. This is generally optimal for stimulation of the motor cortex, but we have previously shown that there is individual variability in the ideal angle for inducing optimal responses when stimulating the DLPFC(45). Therefore, we propose to use computational modeling(46) to account for the impact of each individual's unique head geometry on the E-field at the proposed Talairach-based DLPFC brain target, and use this information to individualize the TMS coil position and orientation as well as the TMS pulse intensity in order to deliver a uniform E-field dose at the target across patients(47). This approach is also supported by preliminary data from MPI Liston showing that E-field modeling improves treatment prediction (see Aim 3).
Summary. we will achieve three target objectives: 1) we will systematically optimize an iTBS protocol to consistently induce long-term plasticity, which is understood to be a key therapeutic mechanism of action; 2) we will compare the efficacy of DLPFC- vs. DMPFC-rTMS for treating anhedonia and determine optimal dosing strategies; and 3) we will identify predictors of response which will be used in Aim 3 to build models for rapidly identifying which individuals will require TMS and which target site is optimal.

Objectives

In Aim 1, we will define novel anhedonic depression subtypes using a battery of fMRI, EEG, and behavioral measures in N=130 MDD patients. Our target objectives are to identify subtypes of anhedonia, anchored in biology, and expected to respond differently to treatment; and to develop algorithms for subtyping most patients based on inexpensive behavioral and clinical measures. In Aims 2 and 3, participants will be randomized to receive a 5-day accelerated course of rTMS targeting the DMPFC or left DLPFC, or sham rTMS. Our target objectives are to 1) optimize iTBS for induction of plasticity; 2) determine the optimal dosing in individual patients and enhance the durability of response; 3) generate models (biomarkers) for predicting response to DLPFC-rTMS vs. DMPFC-rTMS; and 4) integrate these models into a comprehensive system for matching patients to the most individually effective treatment.

Primary Outcome:
We will compare the efficacy of DLPFC-rTMS vs. DMPFC-rTMS vs. sham for treating anhedonia using linear mixed effects models with % change in SHAPS and MADRS as the primary outcomes weekly until 8 weeks after treatment onset.
Hypotheses: (1) SAINT applied to DLPFC and DMPFC will both result in significant reductions in anhedonic symptoms compared to sham, but there will be no meaningful group differences

between the two targets. (2) The minimum effective dose for each target will be less than the full five-day course of treatment, but will differ between the two targets. (3) There will be a relationship between the underlying anhedonic biotypes and the targets, with some biotypes responding more consistently to one target as opposed to the other.

Study Design/Methodology

Phase: Phase 2 Clinical Trial

Trial Design: Randomized, Sham-Controlled, Double-Blinded Study

Methods to Minimize Bias: This study will achieve robust and unbiased results via several design features including: explicit inclusion/exclusion criteria; randomization of intervention condition; the use of a validated sham control; blinding; use of validated laboratory and interview/self-report measures and methods; explicit hypotheses and corresponding planned statistical analyses; power estimates; planned handling of retention/attrition and missing data; and, careful consideration of potential confounds. All experimental details will be reported in a fully transparent manner to support replication.

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

Study Arms: We propose a randomized 3-arm double-blinded parallel experimental trial of 5 days duration in 130 patients with anhedonic depression (~43/arm). This will provide 80% power to detect an effect size of f > 0.27 and 95% power for f > 0.35 for comparing the three trial arms (ANCOVA). All subjects will be randomized to receive one of three treatment arms:

· Arm 1. Accelerated DLPFC-rTMS (SAINT): This group will undergo the standard SAINT protocol: 10X daily iTBS (1800 pulses) x 5 days at 90% RMT, depth-adjusted to PFC atrophy. Personalized rTMS targets will be identified using a hierarchical clustering algorithm to isolate functional subregions of the left DLPFC and sgACC, and locate the optimal DLPFC target, maximally anticorrelated with sgACC
· Arm 2. Accelerated DMPFC-rTMS: This group will receive the same treatment as Arm 1, except we will use a functionally defined DMPFC target, anticorrelated with the sgACC as above.
· Arm 3. Sham DLPFC-rTMS or Sham DMPFC-rTMS: This will be applied using a commercially available sham stimulation system to ensure blinding of the patient and technician / treater. This involves Cool-B-65 A/P (DLPFC) or Cool D-B0 A/P (DMPFC) with one coil side producing active and one side sham stimulation as well as an electrical stimulation system to mimic the TMS sensation during sham stimulation. Sham stimulation will be delivered at standard parameters. Note that the sham condition will be split evenly between sham versions of each target, and that these two shams will also be counterbalanced

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

Name of Study Intervention: Accelerated intermittent theta-burst stimulation (aiTBS)
Interim Analysis: N/A
Stratification: None planned

Study Population

We will screen as many participants as needed until enrollment reaches 130 participants and employ a three-arm design with 43 subjects per arm. If a participant withdraws or is withdrawn from the study prior to completing treatment additional participants will be screened until enrollment reaches 130. The target population is males or females of all ethnicities who are between 18 and 80 years of age with treatment-resistant major depressive disorder who are otherwise in good general health. Participants must be without contraindications to Magnetic Resonance Imaging (MRI) or transcranial magnetic stimulation (TMS) and must be able to attend all study visits. We will use a stratified recruitment strategy to target moderate (~40%), and severe (~40%) anhedonia symptoms (by SHAPS, see below). We enroll N=130 patients with anhedonic depression over the 3-year period. Assuming 12-15% attrition, this sample will provide 95% power to detect fMRI and behavioral predictors of treatment response with at least modest effect sizes ($r > 0.19$). In addition, 20% of subjects will undergo an additional scan on a second day prior to initiating treatment, to evaluate test-retest reliability of fMRI and subtyping metrics. Table 1 summarizes data types and assessment frequency for all three aims.

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

1. Male or Female, between the ages of 18 and 80 at the time of screening.
2. Able to read, understand, and provide written, dated informed consent prior to screening. Proficiency in English sufficient to complete questionnaires / follow instructions during fMRI assessments and aiTBS interventions. Stated willingness to comply with all study procedures, including availability for the duration of the study, and to communicate with study personnel about adverse events and other clinically important information.
3. Currently diagnosed with Major Depressive Disorder (MDD)and meets criteria for a Major Depressive Episode, according to the criteria defined in the Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5).
4. The patient has demonstrated a failure of one or more trials of a pharmacological medication as treatment for MDD.
5. MADRS score of ≥20 at screening (Visit 1).
6. TMS naive.
7. Access to ongoing psychiatric care before and after completion of the study.
8. Must be on a stable antidepressant therapeutic regimen for 6 weeks prior to study enrollment and agree to continue this regimen throughout the study period.
9. In good general health, as evidenced by medical history.

10. For females of reproductive potential: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation.
11. Agreement to adhere to Lifestyle Considerations throughout study duration.

Lifestyle Considerations:

During this study, participants are asked to:
● Abstain from becoming pregnant from the screening visit (Visit 1) until after the final study visit (Visit 10).
● Abstain from caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 3 hours before the start of each dosing session until after the final TMS session.
● Abstain from alcohol for 24 hours before the start of each dosing session until after collection of the final MRI.
● Participants who use tobacco products will be instructed that use of cigarettes will not be allowed during the study.

Exclusion Criteria
An individual who meets any of the following criteria will be excluded from participation in this study:

1. Pregnancy
2. History of or current psychotic disorder or bipolar disorder
3. Severe borderline personality disorder
4. Diagnosis of Intellectual Disability or Autism Spectrum Disorder
5. Primary psychiatric condition other than MDD requiring treatment except stable comorbid anxiety disorder
6. Current moderate or severe substance use disorder or demonstrating signs of acute substance withdrawal
7. Urine screening test positive for illicit substances
8. Acute suicide risk based on clinical judgement or a suicide attempt within the past 6 months
9. Any history of ECT (greater than 8 sessions) without meeting responder criteria
10. Recent (within 4 weeks of any clinical effect) or concurrent use of rapid acting antidepressant agent (i.e., ketamine or a course of ECT)
11. History of significant neurologic disease, including dementia, Parkinson's or Huntington's disease, brain tumor, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma
12. Untreated or insufficiently treated endocrine disorder.
13. Contraindication to receiving rTMS (e.g., metal in head, history of seizure, known brain lesion)
14. Contraindication to MRI (ferromagnetic metal in their body)
15. Treatment with an investigational drug or other intervention within the study period
16. Depth-adjusted aiTBS treatment dose > 65% maximum stimulator output (MSO)

17. Unstable symptoms between screening and baseline as defined by a ≥ 30% change in MADRS score.
18. Any other condition deemed by the PD to interfere with the study or increase risk to the participant

The effects of rTMS on the developing human fetus are unknown(48). Accordingly, we will not be enrolling pregnant women to this study. Women of childbearing potential must agree to use adequate contraception (hormonal / barrier method of birth control or abstinence) prior to study entry and for the duration of study participation. Females of childbearing-age will have a pregnancy test prior to starting the rTMS stimulation course. Should a woman become pregnant or suspects she is pregnant while participating in this study, she should inform study staff.
Participants taking certain psychoactive medications will be assessed for safety by the PD, due to potential for increase of seizure risk(30) and change in cortical excitability(48).

Study Interventions:

Active aiTBS Intervention: We have previously discussed this stimulation approach with the FDA, and the FDA deemed the approach nonsignificant risk (NSR). aiTBS will be delivered similarly to our past(26,41) aiTBS studies using the MagVenture MagPro X100 (Skovlunde, Denmark) TMS device equipped with a Cool-B65 A/P coil or D-B80 A/P coil. The L-DLPFC or DMPFC functional target will be localized for each participant using a Localite TMS Navigator (Localite, Bonn, Germany). Participants will then be treated with 1,800 pulses of iTBS (3-pulse 50-Hz bursts at 5-Hz for 2-second trains, with trains every 10 seconds) per session at 90% resting motor threshold and depth-adjustment to the personalized functional target(49). Each session will last 10 min followed by a 50-minute intersession interval. Ten sessions will be applied per day (18,000 pulses/day) for 5 consecutive days (90,000 total pulses).

Sham aiTBS Intervention: Intervention will be administered with an 'A/P' coil (MagVenture, Denmark) which has both an active and sham side that are identical in appearance. The intervention condition is determined based on a code assigned at randomization. Based on the assigned code the magnetic stimulation is either directed towards or away from the head (i.e., when the randomization code assigns sham stimulation then the magnetic stimulation ends up being directed away from the head). During sham stimulation, however, the magnet still activates. Accordingly, the sound, appearance, and sensation of sham stimulation operation is the same as it is for active stimulation. Thus, there is no way for the operator to know if the patient is getting sham or active stimulation. Similarly, raters will have no knowledge of which ID corresponds to which intervention. This type of sham has been demonstrated to be indistinguishable from real TMS, has been well tolerated(50,51), and successfully used in clinical trials.

Dosing and Administration: We will deliver both active and sham study intervention via a MagPro X100 (MagVenture, Skovlunde, Denmark) TMS. The intervention paradigm consists of

10 daily sessions (50 total over 5 days) of intermittent theta-burst (iTBS) stimulation (3-pulse 50-Hz bursts at 5-Hz for 2-second trains, with trains every 10 seconds), delivered with 50-minute inter-session intervals (10-minute sessions, 50-minutes in between sessions). Stimulation will be delivered at 90% of the resting motor threshold (with depth correction to account for the distance between the scalp and cortex). aiTBS protocol will be administered with a consistent dose escalation across all subjects receiving active stimulation of 18,000 pulses/day and 90,000 pulses/course. An operator entered code (derived from randomization) will instruct the device to deliver active or sham magnetic stimulation.

Custom MATLAB scripts will be used to identify the portion of the DMPFC or left DLPFC maximally anticorrelated with the sgACC, which will serve as the target for both active and sham stimulation. The intervention target will be located via a Localite TMS Navigator (Localite, Bonn, Germany). More specifically, the left dorsolateral prefrontal cortex is located according to routine, FDA-approved clinical rTMS practice. Our scripts then further discern functional subregions within the left DLPFC or DMPFC.

In rare cases in which patients' resting motor threshold for the target stimulation site (foot MT for dmPFC, hand MT for dlPFC) exceeds the maximum stimulation intensity (65% MSO), but whose other MT (hand for dmPFC, foot for dlPFC) is below the max stimulation intensity, patients will be re-randomized to the other stimulation site, maintaining the blind on active vs. sham.

Activities:

Clinical Assessments. We will use the following clinical scales to quantify anhedonia: Snaith-Hamilton Pleasure Scale (SHAPS), Positive Valence Systems Scale 21 Items (PVSS-21), and the Dimensional Anhedonia Rating Scale (DARS). General mood and anxiety will be quantified using the Montgomery Asberg Depression Depression Rating Scale (MADRS), 6 items Hamilton Depression Scale (HAMD-6) Work and Social Adjustment Scale (WSAS), Quick Inventory of Depressive Symptomatology (QIDS), and General Anxiety Disorder-7 (GAD-7).

Treatment response will be quantified by measuring pre- vs. post-treatment changes in anhedonia (SHAPS) and depression (MADRS) as primary outcome measures. As explained above, to determine the minimally effective dose in the 5-day rTMS arms, we will also use a modified daily assessment battery (HAMD-6 & MADRS-S) to identify in a temporally granular fashion at what point in time relief from anhedonia begins to appear.

Behavioral Assessments. We will use two objective behavioral tasks to quantify consummatory and anticipatory hedonics: (1) Bonnelle effort-reward task, and (2) Niv's effort-reward trade-off task. We selected these tools to provide a comprehensive assessment of hedonic function and affective symptoms, and based on prior work showing fMRI correlates.

1 Effort- and reward-based decision-making task (with handgrip) (modified after Bonnelle et al., 2016) (during MRI)

The aim of the Effort- and Reward-based Decision-making Task (also known as the Bonnelle task) is to investigate whether effort or reward is most critically involved in anhedonia observed in healthy individuals (Bonnelle et al., 2016). In this simple computer game, participants are presented on a trial-by-trial basis with an offer, which they can accept or reject. They are presented visually with a combination of a “stake” (or incentive) and an “effort” level. If they accept the offer, they are required to engage in an effortful physical response (i.e., squeezing a handgrip) to obtain a “reward.” As in real-world situations, the actual reward obtained depends both on the stake on offer and on the physical force produced. If an individual rejects the offer, a new offer is presented.

During the Bonnelle task, effort will be measured using a BIOPAC MR-compatible Hand Clench Dynamometer. This hand-held device is MRI compatible. The trace conductive parts of the transducer are electrically and thermally isolated from the subject.

2 Effort-Reward Trade-off Task (Niv/Berwian) [max. 30 min, max 80 trials]

Task description:
The goal of the task is to assess reward and effort anticipation and experience. On each trial, patients decide between investing little effort (fewer button presses) for a small reward (points) or more button presses for a larger reward. Effort levels include 20, 40, 70, 100 and 130 button presses. Rewards include 3,4,5,6 and 7 points. Patients indicate their decision with a button press within 4 sec, and then have 40 sec to execute the effortful behavior, allowing us to measure effort experience. We collect data on the choices subjects make as well as the time it takes them to make the choice (decision time) and the time between button presses (effort execution time). Every third trial participants are asked to rate their momentary happiness on a slider ranging from 0 to 100 which we use as a proxy to assess reward experience.

Effort Reward Task: This task is a behavioral paradigm that offers researchers and clinicians a means to explore effort-based decision-making in humans. On each trial, patients need to decide between investing little effort (few button presses) for a small reward (i.e., points that will be converted into an additional paid bonus) or more button presses for a larger reward. Patients indicate their decision (from which we disentangle the tradeoff between anticipated reward and effort cost) with a button press within 4 sec, and then have 40 sec to execute the effortful behavior, allowing us to measure effort experience. On a subset of trials, participants are asked to rate their momentary happiness which we use as proxy to assess reward experience. DURATION max: 25 min [75 trials]

Participants will partake in one behavioral computer tasks offered by our collaborators at Vanderbilt University. Study participants will receive a unique link that contains within it the participant's subject ID. This link (and subject ID) will be saved by us and our collaborators in Vanderbilt. The link will send participants directly to a website where they can conduct the behavioral tasks. The subject ID embedded in the link allows to match the task data collected by our collaborators at Vanderbilt with the clinical data collected by our study team.

Data storage:
The task is written in javascript and can be run in any modern web browser. The task will be hosted on a server located at Vanderbilt University. The server is encrypted and can only be accessed through dual authentication. The data can only be accessed by our collaborators Yael Niv and Isabel Berwian and authorized members of their team. The Effort Reward Task is written in javascript and can be run in any web browser. The task and data, identified only by a subject ID (random number not related to the true subject's identity at our site) will be hosted on a server located at Vanderbilt University. The server is encrypted and requires authentication to gain access. The data can only be accessed by our collaborators Yael Niv and Isabel Berwian and authorized members of their team.

We will share de-identified data with our collaborator at Vanderbilt Unversity. The data will be encrypted during data transfer.

Procedure:
Study participants will receive a link that contains a random subject ID. This link (and subject ID) will be saved by us and our collaborators in Vanderbilt. The link will send participants directly to a website where they can conduct the behavioral task. The subject ID embedded in the link allows to match the behavioral data collected by our collaborators with the clinical data collected by our study team.

Execution of the task

Participants will receive a link that directs them to the task. All task instructions are integrated in the code and will be automatically presented to the participant.

Neuroimaging. Within 2-3 days of their clinical assessment, all participants will receive an MRI assessment (Siemens Prisma 3T): a) T1 anatomical at 1mm^3 resolution; b) 20-minute multiband, multi-echo resting-state T2* BOLD functional at 2mm isotropic resolution; ~~c) 20-minutes hyperband rs-fMRI and~~ (c) task-based fMRI scan (Bonnelle Effort-Reward Task). All subjects at all sites will receive rsfMRI scans before and immediately after treatment.

EEG. All participants will receive a resting state EEG assessment (64-channel) to generate functional connectivity data that will be used to evaluate whether inexpensive EEG data could be substituted for fMRI measures without degrading subtype predictions (see below).

GeneActiv Watch. This component of the study is optional for subjects. The primary acquisition device for continuous actigraphy will be a wristband provided to participants for the duration of the study to capture activity samples that involve unimanual movements of the upper extremities. It is optional for participants to participate in this part of the study. For this purpose, the GeneActiv actigraphy band (ActivInsights, UK) has several desirable features:

- Performs continuous 3-axis accelerometry, light, and near-body temperature at sampling rates and recording durations that meet both experimental and practical needs (e.g., 10-hz over 45 days, 30-hz over 21 days, or 100-hz over 7 days)
- Participants can press a button on the device to timestamp salient events, which will be key for annotating actigraphy data collection
- Data are provided in raw form to the investigator
- The device has been used at scale for the UK Biobank (~100K individuals) as well as an NIH intramural program (1ZIAMH002954-01 Motor Activity Research Consortium for Health, PI: Kathleen Merikangas), resulting in publicly available data sets and processing pipelines that may be leveraged in this project.

We will use our existing supply of GeneActiv devices and have also requested additional wrist actigraphy devices to meet the needs of the present longitudinal study.

The GeneActiv Original has:

- 3-axis accelerometer: having the capability of being able to see the position in space will also allow us to calculate the acceleration, which will provide the researchers with the magnitude of acceleration (the change in speed per unit time)
- Peripheral skin temperature sensor
- Luminance sensor We will collect the raw data from the device itself, rather than solely proprietary derivatives of raw data using these sensors.

The GeneActiv watches do not contain a microphone, cameras, or any other sensors that could generate identifiable data streams. They also have sufficient battery life and other usability characteristics to minimize discomfort to the participant.

Randomization and Blinding:

In this study, participants will be randomized to active vs. sham aiTBS in a 1:1:1 ratio in randomly selected block sizes of 2, 4, or 6 as based on a random number generator and without stratification. Blinding will be achieved via a sham rTMS coil (Cool-B65 A/P or D-B80 A/P) used with the device (MagPro X100, MagVenture, Skovlunde, Denmark). These coils can deliver either active or sham iTBS in a manner that is randomized by the system itself and therefore blinded to the treater. The sham setting on this coil looks and sounds identical to the active setting but has a hidden aluminum plate blocking actual stimulation. The MagVenture TMS device holds a blinded key code that is kept by the individual that holds the blind. During the rTMS setup, the operator is instructed to flip the coil to correspond with the key code, but the operator is not able to discern the active versus sham stimulation.

For additional blinding of the operator:

- The participant wears a mouth-guard to prevent potential teeth grinding and/or audible noises from the sound of his/her mouth moving from active stimulation.
- Participants will wear headphones that generate the sound of the TMS machine as well as earmuffs to mask the actual noise of the TMS machine.
- The operator will apply lidocaine numbing gel before sessions 1, 3, 5, 7 and 9 to the scalp where the TMS coil is being placed to alleviate active stimulation discomfort.
- The operator will not touch the surface of the coil, as one side may be hotter than the other; knowing which side is hotter or colder can potentially unblind him/her.
- The operator will hang a blinding sheet/cloth over the side of the TMS coil to act as a barrier between him/her and the participant. This prevents the operator from being able to see if there are facial muscle movements, which could indicate active stimulation.
- This protocol has been used to successfully blind participants in our recent RCT(22).

The blinded randomization code will be kept in the individual case report form (CRF), and the key linking the code to the participants condition will be kept separately in an encrypted file, stored outside of the lab and able to be accessed only by a person who has no direct or indirect interaction with participants or data collection. The blind will be maintained until the completion of the study and data-lock is achieved, after which planned unblinding will take place.

Unplanned unblinding will only take place in the unlikely events that either: a) there is concern over adverse events that are more serious / frequent than expected, or; b) on an individual basis when knowing the randomized condition for an individual participant results in improved clinical decision making in an emergency setting. In the case of unplanned unblinding, the Stanford IRB will be informed.

We do not anticipate unintentional unblinding; however, in the event a member of the study team becomes unblinded, we will track this event in the CRF, and all study-team members know to not unblind other study-team members.

Concomitant Therapy:

Participants will be required to continue all psychotropic medications throughout the study period, as they were at the time of screening. Any ongoing psychotherapy that is in a maintenance phase (i.e., not skills training) may be continued, but no new psychotherapy may be initiated during the course of the study.

To ensure adequate sleep each evening prior to TMS intervention (a safety requirement), certain sleep medications (e.g., zolpidem, zaleplon, eszopiclone, quetiapine) may be prescribed by the PD or study MD immediately prior to or during the course of TMS. These medications may be administered up to the night prior to the stimulation session (until midnight), but not during the morning of the sessions or at any time during the intervention day. The use of alternative hypnotics or the short term use of anxiolytic medications (e.g., hydroxyzine, propranolol) during an intervention day requires prior approval from the PD or study MD.

As per clinical standard of care with rTMS, participants are encouraged to bring OTC acetaminophen or ibuprofen for prophylactic use if they are concerned about the potential emergence of adverse events that are commonly experienced with rTMS. Such use would be considered as standard of care. Short-term treatments for other headaches, mild aches/pains, or seasonal allergies will be allowed during the study provided the medications utilized have no established psychotropic effects that might confound interpretation of study outcome measures. These medications may include non-sedating, over-the-counter analgesics or antihistamines.

Rescue Medicine:

No rescue medications will be used

Screen Failure:

Screen failures are defined as participants who sign the screening ICF and/or the study ICF and complete some or all of the screening and/or baseline visit(s) but are not subsequently enrolled in the study due to not meeting study entry criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

Individuals who do not meet the criteria for participation in this study at the time of screening and are deemed screen failures may be rescreened at a later date and considered for trial enrollment. Rescreened participants will be assigned a modified version of the same participant number as for the initial screening (e.g., s001, s001a, s001b, etc.).

Study Intervention Discontinuation and Participant Discontinuation/Withdrawal:

Discontinuation from aiTBS can be classified as temporary or permanent depending on the timing in which it occurs. If the participant has not completed visit 3 (Treatment Day 1) as defined in the Study Schedule, they may qualify for temporary study discontinuation. Temporary discontinuation may result from any COVID-19 related reason or other qualifying reason as deemed appropriate by the PD or their designee. This may be, but is not limited to, temporary study discontinuation while a participant quarantines, receives COVID-19 care, or any other qualifying reason. After receiving health clearance, the participant may resume the study at visit 2 (baseline) if they continue to meet study criteria.

If aiTBS discontinuation occurs after the completion of visit 3, or if a participant chooses to discontinue the study intervention, this will be classified as a permanent study discontinuation. Any participant who discontinues or is withdrawn from the study before the completion of visit 3 (Treatment Day 1) will be replaced.

The data to be collected at the time of permanent study intervention discontinuation will depend on when the discontinuation occurs in the course of the study. Discontinuation information (e.g.,

date and the reason(s) for discontinuation) will be recorded in the subject's CRF (i.e., Study Completion Form) and relevant forms on REDCap. The Protocol Director may also withdraw a subject at any time if he/she believes that for safety reasons it is in the best interest of the subject to be withdrawn.

If the discontinuation occurs prior to the completion of Visit 3 (Treatment Day 1) then information collected will include (if possible) the following:

- Questionnaires about mood and well-being.
- Questions about any adverse events or health problems since the beginning of the study intervention.

If the discontinuation occurs after the completion of Visit 3 (Treatment Day 1), then further data will be collected as possible according to the Intention to Treat principle (see the 'Missing data and attrition' subsection within the 'Statistical Analysis Plan' section for further details).

Subjects withdrawn from the study may be replaced if withdrawal occurs any time prior to study completion so that the per-protocol analysis includes at least the pre planned total of 100 participants. However, any participant who completes the entirety of Visit 3 will be included in the Intention to Treat analysis, as noted above.

The study time commitment and schedule will be thoroughly explained to subjects. Subjects will be encouraged to remain adherent with all expected study visits and advised that non-adherence to expected study visits may result in removal from the study. Study adherence will be clearly discussed and emphasized during the informed consent process and reinforced throughout the study Should a participant fail to return for required visits, drop out of the study, or be lost to follow-up, effort will be made to contact the participant and determine why. This information will subsequently be recorded on the subject's CRF and relevant forms on REDCap.

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study, and the reason for discontinuation will be documented. Reasons for withdraw may include (but are not limited to):

- Pregnancy.
- Significant non-adherence with study procedures.
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- Disease progression which requires discontinuation of the study intervention.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Participant is unable to adhere to the aiTBS schedule for the entire 5 days.
- If an incidental finding is discovered upon imaging that either the study staff (physicians) and/or CNI assigned radiologist deems unsafe or requires medical followup.

- The randomization code is broken for the subject.

Subjects may withdraw voluntarily from the study at any time.

Lost to Follow Up:

A participant will be considered lost to follow-up if he or she fails to return for one scheduled visit and is unable to be contacted by the study staff.

We will take the following actions if a participant fails to return for a required study visit:

- We will attempt to contact the participant and reschedule the missed visit within 24 hours. We will counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if continued study participation is feasible.
- Before a participant is deemed lost to follow-up, the investigator or his designee will make every effort to regain contact with the participant (where possible, 3 telephone calls or emails and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). We will record these contact attempts in REDCap.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with the primary reason of lost to follow-up.

Study Schedule (Table 1):

Procedures	Screening Day 1 Visit 1	Baseline 3-6 days pre treatment Visit 2	Treatment Week (Monday-Friday) Visits 3-7	Immediate post (MRI + EEG + assessments) within 48hrs post treatment Visit 8	4 & 8 Week Post (Friday) Visits 9 & 10 Remote	Week 10 through Week 52 Long-Term Follow-Up	**Open Label Follow Up
CONSENT							
Informed Consent Form 1 (Screening)	X						
Informed Consent Form 2 (Study)		X					X
Capacity to Consent Form		X					X
CLINICIAN ADMINISTERED ASSESSMENTS / SCALES							
Demographics	X						
Diagnostic Clinical Interview + Previous Medical and Psychiatric History	X						
TASS TMS Safety Form	X						
MRI Safety Form	X	X		X			X
BPD diagnostic module from SCID for DSM-5*	X						
Current & Past Medications	X	X		X			X
ATHF - Current	X						

ATHF - Lifetime	X						
SCID Overview	X						
MINI	X						
CSSRS	X						
MADRS-CR	X	X		X			X
Maudsley Staging Method	X						
YMRS	X	X	X	X			X
MSSI	X	X	X	X			X
S/D-IAT		X		X			X
Probabilistic Reward Task, Niv Effort-reward Task		X		X			X
MMSE[a]	X						
CGI-S		X		X			X
CGI-I				X			X
Motor Threshold	X	X					
HAMD-6		X	X				X

SELF-REPORTS							
PSQI	X						
MADRS-S	X	X	X	X	X	X	X
SHAPS	X	X		X	X	X	X
DARS		X		X	X	X	X
PHQ-8		X		X	X	X	X
GAD-7		X		X	X	X	X
BSL-23 and Behavioral Supplement	X	X		X	X	X	X
Work and Social Adjustment Scale (WSAS)		X		X	X	X	X
Positive Valence Systems Scale (PVSS-21)		X		X	X	X	X
QIDS		X		X	X	X	X
Medication Change					X	X	X
NEUROIMAGING ASSESSMENT							
T1 Anatomical		X		X			X
Resting State fMRI Connectivity		X		X			X
Task-based fMRI (Bonnelle)		X		X			X
OTHER ASSESSMENTS / PROCEDURES							
Resting EEG		X		X			X

**rTMS Treatment			X			X	X
Adverse Events			X	X			X
Heart Rate Variability			X				X
Active/Placebo Rating			X (after 1st and 50th session)				
Blood Draw#		X		X			X
Urine Drug Test		X	X	X			X
Urine Pregnancy Test		X					X
COVID-19 Screener		X	X	X			X

Study Schedule Footnotes:

*If a participant has a history of or endorses symptoms of BPD then the diagnostic module will be performed

^If a participant has a history of or endorses symptoms of anxiety then the SCID anxiety module will be performed.

[a]Optional, to be included if there is clinical suspicion for cognitive impairment.

#Optional

- Subjects who have provided screening data for another study in Stanford University's Brain Stimulation Laboratory (BSL) may have their screening data used for this study. Additionally, screening data used in this study may be used in another study in BSL. The purpose of this is to reduce unnecessary burden to the subject. The discretion of which screening data is accepted is up to the discretion of the investigator. A Note-to-file may need to be filed to explain the source and timepoints related to the screening data. Data will be manually re-entered within BSL's RedCap system from the previous study into the new study. **At the discretion of the Protocol Director or their designee, participants who do not demonstrate a treatment response during the main study or experience relapse may be offered a course of open label treatment at a mutually convenient time. These participants will complete the same assessments and procedures as listed in visits 2-10. Adverse events will be identified via a combination of participant report and study team observation. For this optional open-label phase, the time period for AE assessment begins after the first TMS treatment and continues until the end of this phase. AEs noted during this period will be recorded by the PD or their designee and followed until resolution or until medical stability as judged by the PD or their designee.

Adverse Events:

An adverse event (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a person who has received stimulation with a TMS device or undergone an MRI scan. The event need not be causally related to the TMS device or the MRI scan in order to be considered an AE. Designated study personnel may document AEs, and the PD or his designee will evaluate and determine AE severity and relatedness.

An AE includes, but is not limited to:

- Any adverse finding including a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these.
- Any clinically significant worsening of a pre-existing condition;
    - An AE that has been associated with a pre-existing condition is a clinical condition (including a condition being treated) that is diagnosed before an informed consent form is signed and is documented as part of the subject's medical history.

Serious Adverse Events:

A Serious Adverse Event (SAE) is defined as an AE that:

- Results in death
- Is life threatening
    - Life threatening refers to immediate risk of death as the event occurred or use or continued use of the device or other medical product might have resulted in the death per the reporter. A life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death.
- Requires inpatient hospitalization or prolongation of an existing hospitalization
    - Admission to or prolongation of an existing partial hospitalization program (PHP) or intensive outpatient program (IOP), both of which are outpatient programs, are not included in this definition
    - Hospitalization is defined only as an actual admission.
    - Hospitalizations planned before the start of the study, for a preexisting condition that has not worsened, do not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a preexisting condition of osteoarthritis of the knee that has not worsened during the study).
- Results in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life
- Necessitates medical or surgical intervention to preclude such impairment
- Results in a congenital anomaly or birth defect

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered SAEs, based upon appropriate medical judgment as defined by the PD or his designee.

Severity of Event:

All AEs will be assessed by the study clinician using the grading system defined below and recorded on designated REDCap subject-specific and study-wide AE logs.

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Relationship to Study Intervention:

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Causal relationship options and definitions are as follows:

· Definitely related: Event can be fully attributable to administration of the TMS stimulation or the MRI device.

· Probably related: Event is most likely to be explained by administration of the TMS stimulation or MRI device, rather than the subject's clinical state or other agents/therapies.

· Possibly related: Event is as likely explained by administration of the TMS stimulation or MRI device, as by the subject's clinical state or other agents/therapies.

· Probably not related: Event is most likely to be explained by the subject's clinical state or other agents/therapies, rather than the TMS stimulation or MRI device.

· Definitely not related: Event can be fully explained by the subject's clinical state or other agents/therapies, rather than the TMS stimulation or MRI device.

The questions concerning whether the condition existed before the start of the intervention phase of the study and whether it has increased in severity and/or frequency will be used to determine the relationship to study intervention.

When assessing the relationship between an investigational product/protocol and an AE, the following parameters are considered:

· Temporal relationship between the TMS device/protocol and the AE

· Biologic plausibility of relationship

· Subjects' underlying clinical state or concomitant agents/therapies

· Where applicable, whether the AE abates on discontinuation of the TMS device or MRI device (de-challenge)

· Where applicable, whether the AE reappears on repeat exposure to the TMS device or MRI device (re-challenge)

Expectedness:

In the table above, there is a list of common, expected AEs(19). Worsening of any symptoms of depression or related to depression also is an expected AE, as could be the case for any clinical trial of a novel therapy, particularly when there is a sham control condition as in our case. Furthermore, any iTBS study has a risk of mania and hypomania as an expected adverse event. If an unexpected AE occurs, or if a common AE occurs with severity greater than that expected, the participant will be further evaluated by a member of the study team with formal medical training.

Adverse Event Assessment and Time Period:

All subjects will have telephone and email contact information to reach the protocol director and the Stanford IRB, in case of any distress or adverse response to the rTMS or other components of the study. Additionally, AEs will be monitored continuously by designated study staff and recorded in applicable subject-specific and study-wide REDCap eCRFs. Research staff will be trained to attend to signs of AEs and to report any potential unrelated or unexpected AE immediately to the PD or his designee. If AEs occur, appropriate medical and/or psychiatric care will be facilitated for the research participant, and recorded in the appropriate electronic AE logs on REDCap.

AEs will be systematically screened for at the start and end of every visit beginning at the treatment phase of the study. They will be screened for via the following standardized questions that will be asked by research staff:

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

Any positive response(s) to the above questions will be documented electronically and further investigated as appropriate. Any documented AE will be asked about at each subsequent AE assessment until it resolves or through the time frame specified above.

For this study, the time period for AE assessment begins after first study intervention and continues until 30 days following the last day of study intervention. AEs noted during this period will be recorded by the PD or his designee and followed until resolution or until medical stability as judged by the PD or his designee. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode. Follow up will be documented in the subject's study file.

Adverse Event and Serious Adverse Event Reporting:

As per Stanford IRB requirements, AEs will be reported to the IRB annually.

Any unanticipated SAE, regardless of causal relationship, will be reported to the Institutional Review Board (IRB), within 10 business days (5 business days for an unexpected and related death or life-threatening situation) of the PD or his designee learning of the event, by submitting a completed serious adverse event form to the assigned IRB panel. All SAEs will be recorded in subject specific AE/SAE forms on REDCap.

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

Events of Special Interest:

An adverse event of special interest is a device-specific adverse event designated by the PD for transmission in the same time frame as an SAE, even if it does not meet serious reporting criteria. For this protocol, seizure should be reported as an adverse event of special interest.
This includes:

- Seizure
- Pregnancy occurring during the study period in which the subject was exposed to the TMS device;
- Overdose (e.g., a dose higher than that prescribed by a healthcare professional for clinical reasons) with or without AEs;
- Abuse (e.g., use for non-clinical reasons) with or without an AE;
- Inadvertent or accidental exposure with or without an AE;
- Device malfunction that would likely result in death, serious injury or another significant adverse event.

Reporting Events to Participants:

We will closely monitor AE's on a continuous basis and will assess whether any AE is unexpected or more severe than expected (at a rate greater than what would be expected by chance). Should we identify any AE that meets one of those two criteria, or should we have any unexpected SAE's, we will notify currently enrolled participants and change our consent to include the pertinent information.

Safety Oversight:

Safety oversight will be under the direction of the Protocol Director.

Safety Analyses:

We will inquire about AE's at each visit as described above. AE's will initially be inquired about by clinical research coordinators and may then be assessed by study physicians during the same visit. The study physician or their designee in charge of assessing a given AE will provide a thorough description of the event in the participant's CRF and the AE will be followed. The study physician will specifically report on start date, stop date, severity, relationship, expectedness, outcome, and duration, as well as whether or not the AE meets criteria for a SAE. AE's will be coded based upon Medical Dictionary for Regulatory Activities (MedDRA) criteria, coded only once per participant (e.g. should a participant have a headache at each visit only a single headache AE will be coded), and compiled. Once data lock and unblinding has occurred, safety data will be compared between active and sham aiTBS using chi-squared tests (or Fisher's exact test if indicated).

Clinical Monitoring:

Safety oversight of this study will be under the direction of the Protocol Director. We will hold internal monthly meetings to review study recruitment, enrollment numbers, AE/SAEs, and overall study progress. All participant safety data will be captured in eCRFs. Study psychiatrists will review participant eCRFs periodically to ensure adequate clinical monitoring (Dr. Gregory Sahlem and Dr. Ian Kratter).

Statistical Analysis Plan:

Power Analysis: In our previous study we observed an 88% reduction in mean MADRS with scores falling from a mean of 37.71±7.24 (Mean±SD) to 4.65±6.46, which is associated with a very large effect size of 3.3 (Cohen's d). For a paired t-test, and a power of 0.80, this indicates only 3 participants would be required for each arm. To make this estimate more conservative, let us compare our aiTBS effects to the highest responses to sham rTMS for depression we could locate in the literature. Yesavage et al (2018) observed a reduction in MADRS from a baseline of 26.2±6.9 to 13.1±10.5(53) with a course of sham rTMS. Even if we ignore that our aiTBS subjects were significantly more depressed and more treatment resistant, and we just consider the final MADRS score immediately following the end of treatment, the effect size is still 0.97. Thus, for an alpha of 0.05 and a power of 0.80 and powering for an independent-measures t-test, only 18 participants would be required for each arm. Power analysis for one of our biological measures (change in resting-state functional connectivity from baseline to immediate post treatment) yields a requirement of 40 participants in each arm. Considering a ~25% attrition rate (combined participants lost to follow-up and unusable or missing scans), we plan to recruit 50 participants in each arm, as this is far larger than the 18 per arm that is required to power for a significant reduction in MADRS.

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

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

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

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

models converge on real solutions. All post-hoc pairwise comparisons will be Bonferroni-corrected for multiple comparison.

General approach considerations: Primary analysis models will be reported both unadjusted and adjusted for significant clinical covariates. All statistical analysis will be conducted using SAS/STAT version 9.4 (SAS Institute Inc. 2015. SAS® 9.4 Statements: Reference, Fourth Edition. Cary, NC: SAS Institute Inc.). All statistical analyses will be overseen by our biostatistician Dr. Booil Jo, an associate professor in the Stanford department of psychiatry and behavioral sciences - Center for Interdisciplinary Brain Sciences Research. Dr. Jo holds a PhD in Applied Statistics from UCLA and is a leading expert in statistical analysis of mental health research.
Missing data and attrition: Missing data in longitudinal studies can be a problematic feature but will be mitigated through study design considerations. In an attempt to minimize missing data and study attrition, study simplification and enhanced communication between study staff and participants will be emphasized throughout study participation. We will make every effort to prevent attrition by sending phone/text visit reminders, providing participation compensation for time and travel, and reinforcing adherence to the study protocol at each visit.
We will complete both an ITT and a per-protocol (i.e., full study completion) analysis. The ITT will include all study participants who receive at least one full day of intervention and associated assessments (i.e., complete Visit 3 assessments). In keeping with the Intent to Treat Principle for these participants, we will make every effort to continue assessments for the entire course of randomized treatment, even among those who stop participating in the study assigned intervention. In cases of missing data, the last observation carried forward will be utilized.
Informed Consent Process:

Consent/Assent and other informational documents provided to the participant: Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol:

Two signed consent forms will be obtained from each participant: (1) Screening consent form and (2) Study consent form. These consent forms will be administered either in person or electronically.

Consent procedures and documentation: Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The study investigator or his designee will explain the research study to the participant and answer any questions that may arise in a private setting. A verbal explanation will be provided in English of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time,

without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

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

Education and Informed Consent Process: Consent forms will be Institutional Review Board (IRB)-approved, and the participant will be asked to read and review the document. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The signature will be obtained as described above. The consent process will start with an introductory paragraph that describes the study. This statement will be followed by a description of the purpose of the research. The participant will be informed that this is a double-blinded study, they have a 50% chance of receiving active stimulation, and that their participation is voluntary. Next, the duration of study involvement and the procedures involved will be described.

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

Finally, after reading the experimental subjects' bill of rights, the participant will be asked for their signature in order to consent and give permission to be in the research study. To ensure the participant has capacity to consent, as part of this process the study psychiatrist or their designee will complete a Capacity to Consent form.

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

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

Risk/Benefit:

Given the high degree of safety of rTMS(30), there is a low risk to high benefit ratio for this intervention. rTMS will be performed and monitored according to widely accepted principles that maximize safety(30). Based on our previous open-label studies(26,34), many of the research participants who receive active aiTBS are likely to achieve rapid improvements in their depression symptoms, with associated improvement in their social and occupational functioning.

Primary discomfort in this study may be the device (GeneActiv Watch) itself may become uncomfortable, at which point the participant can notify staff and either remove the device or place at another site on the body. Participants may become more generally uncomfortable with having a device tracking their behavior; in such circumstances, clinical and study staff will attempt to discuss these concerns with the participant, reminding them that we are not permitted to record geospatial location, audio, video, or any information that could allow the individual to be identified from data obtained on the device. If participants remain concerned about this issue, they can withdraw from the study at any time. Primary risk in the study is breach of confidentiality, which would only occur in the event of personally identifiable information from the medical record being inadvertently disclosed to a third-party. As noted above, no identifiable data will be shared with our outside collaborator or available to the device manufacturer.

Study Timeline:

The entire project is estimated to take approximately 36 months, broken down into 24 months of data collection and an additional 12 months of analysis. The total duration for each participant from the time of baseline assessment to study completion (for the purposes of our primary and secondary aims) is approximately 1 month.

In order to acquire additional data on durability of treatment response, participants who meet criteria for response or remission according to the MADRS-CR at the 30-day follow up will continue to be followed biweekly with self-assessments until their PHQ-8 ≥ 10 for two consecutive assessments, a psychiatric consult for a rapid-acting antidepressant treatment occurs, or they are lost to follow-up.

References:

1. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, et al. The Epidemiology of Major Depressive DisorderResults From the National Comorbidity Survey Replication (NCS-R). JAMA [Internet]. 2003 Jun 18;289(23):3095–105. Available from: https://doi.org/10.1001/jama.289.23.3095
2. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. American Journal of Psychiatry [Internet]. 2006 Nov 1;163(11):1905–17. Available from: https://ajp.psychiatryonline.org/doi/abs/10.1176/ajp.2006.163.11.1905
3. Pizzagalli DA. Depression, stress, and anhedonia: toward a synthesis and integrated model. Annual review of clinical psychology [Internet]. 2014;10:393–423. Available from: https://pubmed.ncbi.nlm.nih.gov/24471371
4. McMakin DL, Olino TM, Porta G, Dietz LJ, Emslie G, Clarke G, et al. Anhedonia predicts poorer recovery among youth with selective serotonin reuptake inhibitor treatment-resistant depression. Journal of the American Academy of Child and Adolescent Psychiatry [Internet]. 2012/03/03. 2012 Apr;51(4):404–11. Available from: https://pubmed.ncbi.nlm.nih.gov/22449646
5. Downar J, Geraci J, Salomons T v, Dunlop K, Wheeler S, McAndrews MP, et al. Anhedonia and Reward-Circuit Connectivity Distinguish Nonresponders from Responders to Dorsomedial Prefrontal Repetitive Transcranial Magnetic Stimulation in Major Depression. Biological Psychiatry [Internet]. 2014;76(3):176–

85. Available from:
https://www.sciencedirect.com/science/article/pii/S0006322313010342
6. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multisite Randomized Controlled Trial. Biological Psychiatry [Internet]. 2007;62(11):1208–16. Available from:
https://www.sciencedirect.com/science/article/pii/S0006322307001461
7. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. The Lancet [Internet]. 2018;391(10131):1683–92. Available from:
https://www.sciencedirect.com/science/article/pii/S0140673618302952
8. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nature medicine [Internet]. 2016/12/05. 2017 Jan;23(1):28–38. Available from: https://pubmed.ncbi.nlm.nih.gov/27918562
9. Cárdenas-Morales L, Nowak DA, Kammer T, Wolf RC, Schönfeldt-Lecuona C. Mechanisms and Applications of Theta-burst rTMS on the Human Motor Cortex. Brain Topography [Internet]. 2010;22(4):294–306. Available from:
https://doi.org/10.1007/s10548-009-0084-7
10. Paulus W. Toward Establishing a Therapeutic Window for rTMS by Theta Burst Stimulation. Neuron [Internet]. 2005;45(2):181–3. Available from:
https://www.sciencedirect.com/science/article/pii/S0896627305000152
11. Chung SW, Sullivan CM, Rogasch NC, Hoy KE, Bailey NW, Cash RFH, et al. The effects of individualised intermittent theta burst stimulation in the prefrontal cortex: A TMS-EEG study. Human brain mapping [Internet]. 2018/09/25. 2019 Feb 1;40(2):608–27. Available from: https://pubmed.ncbi.nlm.nih.gov/30251765
12. Li C-T, Chen M-H, Juan C-H, Huang H-H, Chen L-F, Hsieh J-C, et al. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. Brain [Internet]. 2014 Jul 1;137(7):2088–98. Available from: https://doi.org/10.1093/brain/awu109
13. Chistyakov A v, Rubicsek O, Kaplan B, Zaaroor M, Klein E. Safety, tolerability and preliminary evidence for antidepressant efficacy of theta-burst transcranial magnetic stimulation in patients with major depression. International Journal of Neuropsychopharmacology [Internet]. 2010 Apr 1;13(3):387–93. Available from: https://doi.org/10.1017/S1461145710000027
14. Oberman L, Edwards D, Eldaief M, Pascual-Leone A. Safety of theta burst transcranial magnetic stimulation: a systematic review of the literature. Journal of clinical neurophysiology : official publication of the American

Electroencephalographic Society [Internet]. 2011 Feb;28(1):67–74. Available from: https://pubmed.ncbi.nlm.nih.gov/21221011
15. Helfrich RF, Knepper H, Nolte G, Strüber D, Rach S, Herrmann CS, et al. Selective modulation of interhemispheric functional connectivity by HD-tACS shapes perception. PLoS biology [Internet]. 2014 Dec 30;12(12):e1002031–e1002031. Available from: https://pubmed.ncbi.nlm.nih.gov/25549264
16. Thut G, Veniero D, Romei V, Miniussi C, Schyns P, Gross J. Rhythmic TMS causes local entrainment of natural oscillatory signatures. Current biology : CB [Internet]. 2011/06/30. 2011 Jul 26;21(14):1176–85. Available from: https://pubmed.ncbi.nlm.nih.gov/21723129
17. Cole EJ, Stimpson KH, Bentzley BS, Gulser M, Cherian K, Tischler C, et al. Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression. American Journal of Psychiatry [Internet]. 2020 Apr 7;177(8):716–26. Available from: https://doi.org/10.1176/appi.ajp.2019.19070720
18. Holtzheimer 3rd PE, McDonald WM, Mufti M, Kelley ME, Quinn S, Corso G, et al. Accelerated repetitive transcranial magnetic stimulation for treatment-resistant depression. Depression and anxiety [Internet]. 2010 Oct;27(10):960–3. Available from: https://pubmed.ncbi.nlm.nih.gov/20734360
19. Cash RFH, Zalesky A, Thomson RH, Tian Y, Cocchi L, Fitzgerald PB. Subgenual Functional Connectivity Predicts Antidepressant Treatment Response to Transcranial Magnetic Stimulation: Independent Validation and Evaluation of Personalization. Biological Psychiatry [Internet]. 2019;86(2):e5–7. Available from: https://www.sciencedirect.com/science/article/pii/S0006322318320596
20. Weigand A, Horn A, Caballero R, Cooke D, Stern AP, Taylor SF, et al. Prospective Validation That Subgenual Connectivity Predicts Antidepressant Efficacy of Transcranial Magnetic Stimulation Sites. Biological psychiatry [Internet]. 2017/11/10. 2018 Jul 1;84(1):28–37. Available from: https://pubmed.ncbi.nlm.nih.gov/29274805
21. Williams NR, Sudheimer KD, Bentzley BS, Pannu J, Stimpson KH, Duvio D, et al. High-dose spaced theta-burst TMS as a rapid-acting antidepressant in highly refractory depression. Brain : a journal of neurology [Internet]. 2018 Mar 1;141(3):e18–e18. Available from: https://pubmed.ncbi.nlm.nih.gov/29415152
22. Cole EJ, Phillips AL, Bentzley BS, Stimpson KH, Nejad R, Barmak F, et al. Stanford Neuromodulation Therapy (SNT): A Double-Blind Randomized Controlled Trial. American Journal of Psychiatry [Internet]. 2021 Oct 29;appi.ajp.2021.20101429. Available from: https://doi.org/10.1176/appi.ajp.2021.20101429
23. Heijnen WT, Birkenhäger TK, Wierdsma AI, van den Broek WW. Antidepressant Pharmacotherapy Failure and Response to Subsequent Electroconvulsive Therapy: A Meta-Analysis. Journal of Clinical

Psychopharmacology [Internet]. 2010;30(5). Available from: https://journals.lww.com/psychopharmacology/Fulltext/2010/10000/Antidepressant_Pharmacotherapy_Failure_and.20.aspx
24. Alexander L, Gaskin PLR, Sawiak SJ, Fryer TD, Hong YT, Cockcroft GJ, et al. Fractionating Blunted Reward Processing Characteristic of Anhedonia by Over-Activating Primate Subgenual Anterior Cingulate Cortex. Neuron [Internet]. 2018/12/04. 2019 Jan 16;101(2):307-320.e6. Available from: https://pubmed.ncbi.nlm.nih.gov/30528065
25. Rea E, Rummel J, Schmidt TT, Hadar R, Heinz A, Mathé AA, et al. Anti-Anhedonic Effect of Deep Brain Stimulation of the Prefrontal Cortex and the Dopaminergic Reward System in a Genetic Rat Model of Depression: An Intracranial Self-Stimulation Paradigm Study. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation [Internet]. 2014 Jan 1;7(1):21–8. Available from: https://doi.org/10.1016/j.brs.2013.09.002
26. Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH. Subcallosal Cingulate Gyrus Deep Brain Stimulation for Treatment-Resistant Depression. Biological Psychiatry [Internet]. 2008;64(6):461–7. Available from: https://www.sciencedirect.com/science/article/pii/S0006322308007038
27. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep Brain Stimulation for Treatment-Resistant Depression. Neuron [Internet]. 2005;45(5):651–60. Available from: https://www.sciencedirect.com/science/article/pii/S089662730500156X
28. Lozano AM, Giacobbe P, Hamani C, Rizvi SJ, Kennedy SH, Kolivakis TT, et al. A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression: Clinical article. Journal of Neurosurgery JNS [Internet]. 2012;116(2):315–22. Available from: https://thejns.org/view/journals/j-neurosurg/116/2/article-p315.xml
29. Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodesser D, Axmacher N, et al. Deep Brain Stimulation to Reward Circuitry Alleviates Anhedonia in Refractory Major Depression. Neuropsychopharmacology [Internet]. 2008;33(2):368–77. Available from: https://doi.org/10.1038/sj.npp.1301408
30. Dandekar MP, Saxena A, Scaini G, Shin JH, Migut A, Giridharan VV, et al. Medial Forebrain Bundle Deep Brain Stimulation Reverses Anhedonic-Like Behavior in a Chronic Model of Depression: Importance of BDNF and Inflammatory Cytokines. Molecular Neurobiology [Internet]. 2019;56(6):4364–80. Available from: https://doi.org/10.1007/s12035-018-1381-5
31. Bodén R, Bengtsson J, Thörnblom E, Struckmann W, Persson J. Dorsomedial prefrontal theta burst stimulation to treat anhedonia, avolition, and blunted affect in schizophrenia or depression – a randomized controlled trial.

Journal of Affective Disorders [Internet]. 2021;290:308–15. Available from: https://www.sciencedirect.com/science/article/pii/S0165032721003852
32. Light SN, Bieliauskas LA, Taylor SF. Measuring change in anhedonia using the “Happy Faces” task pre- to post-repetitive transcranial magnetic stimulation (rTMS) treatment to left dorsolateral prefrontal cortex in Major Depressive Disorder (MDD): relation to empathic happiness. Translational psychiatry [Internet]. 2019 Sep 3;9(1):217. Available from: https://pubmed.ncbi.nlm.nih.gov/31481688
33. Pettorruso M, Spagnolo PA, Leggio L, Janiri L, di Giannantonio M, Gallimberti L, et al. Repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex may improve symptoms of anhedonia in individuals with cocaine use disorder: A pilot study. Brain Stimulation [Internet]. 2018;11(5):1195–7. Available from: https://www.sciencedirect.com/science/article/pii/S1935861X18301657
34. Avissar M, Powell F, Ilieva I, Respino M, Gunning FM, Liston C, et al. Functional connectivity of the left DLPFC to striatum predicts treatment response of depression to TMS. Brain stimulation [Internet]. 2017/07/13. 2017;10(5):919–25. Available from: https://pubmed.ncbi.nlm.nih.gov/28747260
35. Engel AK, Singer W. Temporal binding and the neural correlates of sensory awareness. Trends in Cognitive Sciences [Internet]. 2001;5(1):16–25. Available from: https://www.sciencedirect.com/science/article/pii/S1364661300015680
36. Canolty RT, Knight RT. The functional role of cross-frequency coupling. Trends in cognitive sciences [Internet]. 2010 Nov;14(11):506–15. Available from: https://pubmed.ncbi.nlm.nih.gov/20932795
37. Noda Y, Zomorrodi R, Daskalakis ZJ, Blumberger DM, Nakamura M. Enhanced theta-gamma coupling associated with hippocampal volume increase following high-frequency left prefrontal repetitive transcranial magnetic stimulation in patients with major depression. International Journal of Psychophysiology [Internet]. 2018;133:169–74. Available from: https://www.sciencedirect.com/science/article/pii/S0167876018302186
38. Noda Y, Zomorrodi R, Saeki T, Rajji TK, Blumberger DM, Daskalakis ZJ, et al. Resting-state EEG gamma power and theta–gamma coupling enhancement following high-frequency left dorsolateral prefrontal rTMS in patients with depression. Clinical Neurophysiology [Internet]. 2017;128(3):424–32. Available from: https://www.sciencedirect.com/science/article/pii/S1388245717300032
39. Sun Y, Giacobbe P, Tang CW, Barr MS, Rajji T, Kennedy SH, et al. Deep Brain Stimulation Modulates Gamma Oscillations and Theta–Gamma Coupling in Treatment Resistant Depression. Brain Stimulation [Internet]. 2015;8(6):1033–42.

Available from:
https://www.sciencedirect.com/science/article/pii/S1935861X15010128
40. Nikolin S, Martin D, Loo CK, Iacoviello BM, Boonstra TW. Assessing neurophysiological changes associated with combined transcranial direct current stimulation and cognitive-emotional training for treatment-resistant depression. European Journal of Neuroscience [Internet]. 2020 May 1;51(10):2119–33. Available from: https://doi.org/10.1111/ejn.14656
41. Tremblay S, Rogasch NC, Premoli I, Blumberger DM, Casarotto S, Chen R, et al. Clinical utility and prospective of TMS–EEG. Clinical Neurophysiology [Internet]. 2019;130(5):802–44. Available from:
https://www.sciencedirect.com/science/article/pii/S138824571930001X
42. Kozel FA, Nahas Z, deBrux C, Molloy M, Lorberbaum JP, Bohning D, et al. How Coil–Cortex Distance Relates to Age, Motor Threshold, and Antidepressant Response to Repetitive Transcranial Magnetic Stimulation. The Journal of Neuropsychiatry and Clinical Neurosciences [Internet]. 2000 Aug 1;12(3):376–84. Available from: https://doi.org/10.1176/jnp.12.3.376
43. Thielscher A, Opitz A, Windhoff M. Impact of the gyral geometry on the electric field induced by transcranial magnetic stimulation. NeuroImage [Internet]. 2011;54(1):234–43. Available from:
https://www.sciencedirect.com/science/article/pii/S1053811910010347
44. Aberra AS, Wang B, Grill WM, Peterchev A v. Simulation of transcranial magnetic stimulation in head model with morphologically-realistic cortical neurons. Brain stimulation [Internet]. 2019/10/07. 2020;13(1):175–89. Available from:
https://pubmed.ncbi.nlm.nih.gov/31611014
45. Thomson RH, Cleve TJ, Bailey NW, Rogasch NC, Maller JJ, Daskalakis ZJ, et al. Blood Oxygenation Changes Modulated by Coil Orientation During Prefrontal Transcranial Magnetic Stimulation. Brain Stimulation [Internet]. 2013;6(4):576–81. Available from:
https://www.sciencedirect.com/science/article/pii/S1935861X12002070
46. Deng Z-D, Lisanby SH, Peterchev A v. Electric field depth-focality tradeoff in transcranial magnetic stimulation: simulation comparison of 50 coil designs. Brain stimulation [Internet]. 2012/03/21. 2013 Jan;6(1):1–13. Available from:
https://pubmed.ncbi.nlm.nih.gov/22483681
47. Balderston NL, Roberts C, Beydler EM, Deng Z-D, Radman T, Luber B, et al. A generalized workflow for conducting electric field-optimized, fMRI-guided, transcranial magnetic stimulation. Nature protocols [Internet]. 2020/09/30. 2020 Nov;15(11):3595–614. Available from: https://pubmed.ncbi.nlm.nih.gov/33005039
48. Cao B, Park C, Subramaniapillai M, Lee Y, Iacobucci M, Mansur RB, et al. The Efficacy of Vortioxetine on Anhedonia in Patients With Major Depressive

Disorder. Frontiers in psychiatry [Internet]. 2019 Jan 31;10:17. Available from: https://pubmed.ncbi.nlm.nih.gov/30766492
49. Alexander L, Gaskin PLR, Sawiak SJ, Fryer TD, Hong YT, Cockcroft GJ, et al. Fractionating Blunted Reward Processing Characteristic of Anhedonia by Over-Activating Primate Subgenual Anterior Cingulate Cortex. Neuron [Internet]. 2018/12/04. 2019 Jan 16;101(2):307-320.e6. Available from: https://pubmed.ncbi.nlm.nih.gov/30528065
50. Glasser MF, Coalson TS, Robinson EC, Hacker CD, Harwell J, Yacoub E, et al. A multi-modal parcellation of human cerebral cortex. Nature [Internet]. 2016/07/20. 2016 Aug 11;536(7615):171–8. Available from: https://pubmed.ncbi.nlm.nih.gov/27437579
51. Tran P, Skolnick P, Czobor P, Huang NY, Bradshaw M, McKinney A, et al. Efficacy and tolerability of the novel triple reuptake inhibitor amitifadine in the treatment of patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. Journal of Psychiatric Research [Internet]. 2012;46(1):64–71. Available from: https://www.sciencedirect.com/science/article/pii/S0022395611001890
52. Daskalakis ZJ, Christensen BK, Fitzgerald PB, Roshan L, Chen R. The mechanisms of interhemispheric inhibition in the human motor cortex. The Journal of physiology [Internet]. 2002 Aug 15;543(Pt 1):317–26. Available from: https://pubmed.ncbi.nlm.nih.gov/12181302
53. Yesavage JA, Fairchild JK, Mi Z, Biswas K, Davis-Karim A, Phibbs CS, et al. Effect of Repetitive Transcranial Magnetic Stimulation on Treatment-Resistant Major Depression in US Veterans: A Randomized Clinical Trial. JAMA psychiatry [Internet]. 2018 Sep 1;75(9):884–93. Available from: https://pubmed.ncbi.nlm.nih.gov/29955803
54. Association, A. P. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). (American Psychiatric Pub, 2013).
55. Berwian, I. M. et al. Computational mechanisms of effort and reward decisions in patients with depression and their association with relapse after antidepressant discontinuation. JAMA psychiatry (2020).
56. Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. Biol Psychiatry. 2005; 57(4):319-27.
57. Vrieze E, Pizzagalli DA, Demyttenaere K, Hompes T, Sienart P, de Boer P, Schmidt M, Claes S. Reduced reward learning predicts outcome in major depressive disorder. Biol Psychiatry. 2013; 73(7), 639-645.