Establishing Functional Biomarkers for Spaced Theta-Burst Stimulation

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a. Brief Summary

We plan to use functional magnetic resonance imaging (fMRI) methods to assess brain changes following transcranial magnetic stimulation (rTMS), in 30 healthy participants. An additional 30 healthy controls will undergo an MRI scan, without use of rTMS or TBS. We will offer these 30 healthy controls an optional component involving 2 sessions of 3-10min of TBS, 1 session on the Magventure TMS device and 1 session on the Nextstim TMS device, in order to compare participant preference between the 2 TMS systems.

For the 30 healthy participants in the MRI+rTMS group, we will assess MRI scans following either/both standard rTMS or TBS (theta-burst stimulation- a novel form of transcranial magnetic stimulation, in participants. We will measure the effects of TMS applied to the motor cortex, a system that when stimulated produces a readily observable behavioral response (e.g., movement of a given body regions). We will also measure the effects of TMS applied to the dorsolateral prefrontal cortex, a target recognized for its anti-depressant effects.

Our goal is to determine how brain activity and blood flow during tasks and at rest change following the applications of TMS to the motor cortex and/or dorsolateral prefrontal cortex.

This study will provide an understanding of the functional brain and behavioral changes that occur following TMS.

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b. Objectives

Please note TMS/TBS are used interchangeably in this protocol as they refer to different settings on the same device, a transcranial magnetic stimulation device, and both types of settings will be used for this study.

This study proposes to: 1 - determine the heart rate changes that are seen with TMS stimulation. 2- determine the optimal burst frequency for TMS, 3-determine the optimal intersession interval for TMS, 4- compare the results of #1 and #2 in the same subjects, 5-determine the effect of TMS/TBS on the resting state functional connectivity. 6- in healthy participants, assess the regulation of neuroplasticity by affective state.

Aim 1: To determine the heart rate changes seen with TMS/TBS.

Hypothesis 1: Heart rate changes will be observed following stimulation.

Aim 2: To determine the optimal burst frequency.

Hypothesis 2: For cTBS, the optimal frequency will be 30Hz bursts at 6Hz while iTBS will be the traditional 50Hz bursts at 5Hz.

Aim 3: To determine the optimal intersession interval for spaced TBS.

Hypothesis 3: For cTBS, the optimal ISI will be 15 min while with iTBS the optimal ISI will be 30 min.

Aim 4: To determine the effect of spaced TBS on the resting state functional connectivity.

Hypothesis 4: Optimized spaced iTBS and cTBS will produce changes in the resting state functional connectivity between pre-motor and motor cortex. Those who have less fc change from iTBS will experience maximal cTBS change in fc (correlated with change in MEP) and vice versa.

Aim 5: To determine the effect of TMS/TBS on the resting state functional connectivity.

Aim 6: To assess the regulation of neuroplasticity by affective state in healthy control participants.

Hypothesis 6: Changes in amplitude and frequency band power of ERP responses to emotional faces following iTBS and cTBS will be differentially affected by different induced affective states. Changes in MEP amplitude following iTBS and cTBS will be differentially affected by different induced affective states.

This study has broad implications ranging from advancing our understanding of the basic mechanisms of TBS on brain function, cerebral blood flow, and pain perception and therapeutic implications that could impact classical rTMS treatment schedules based on the duration of effects of spaced TBS.

c. Rationale for Research in Humans

We are investigating the neural underpinnings and behavioral effects of brain stimulation in humans. As such, only human subjects can be used for this project.

2. STUDY PROCEDURES

a. Procedures

The study will consist of 4 experiments.

PARTICIPANTS

We will recruit 60 healthy controls for this study 30 participants in MRI+rTMS/TBS group and 30 participants in MRI only group. Participants will be 18-80 year-old right handed male and female with no history of psychiatric or neurological diagnoses and no current use of psychoactive medications. They will be recruited to participate in this study, all of whom will be blinded to the purpose of the study. All subjects will be screened for any contraindications to TMS and will give their informed written consent prior to participation.

HEALTHY CONTROLS: MRI ONLY GROUP

30 healthy controls will undergo an MRI scan, without use of rTMS or TBS. We will offer these 30 healthy controls an optional component involving 2 sessions of 3- 10min of TBS, 1 session on the Magventure TMS device and 1 session on the Nextstim TMS device, in order to compare participant preference between the 2 TMS systems.

EXPERIMENT 1: Heart rate changes

The first experiment will determine what heart rate changes are seen following TMS/TBS stimulation. Please note some participants will only be included in experiment 1, availability and scheduling permitting. Subjects will attend 2 sessions where they will receive TMS/iTBS at 70 -100 of active or resting MT, as determined by the investigator. They will receive either active or sham during a session, and the sessions will be in a randomly assigned order.

Stimulation may be applied to the vertex, Beam F3 location, or location determined by neuronavigation. These are all standard locations for stimulation. Various heart rate measurements and cortisol and/or other lab tests will be collected before and after stimulation. fMRI will be completed before and after stimulation. Various questionnaires (e.g. regarding mood will be collected before/after stimulation). Tasks designed to induce mild mental stress (e.g. mental math or similar) will be used during the experiment to create equivalent baseline conditions for all subjects.

EXPERIMENT 2: Optimal Burst Frequency

This next experiment will determine the optimal burst frequency for TBS, comparing iTBS30, iTBS50, cTBS30, and cTBS50 within the same individual. This experiment is an important stepping stone for the overall study, as it will determine how responses to cTBS and iTBS are linked. Subjects will attend four sessions no <4 days apart, receiving the cTBS50, cTBS30, iTBS50, and iTBS30 applied at 80 of RMT. The order in which they will receive each paradigm will be randomized between subjects. In all sessions, MEP recruitment curves will be recorded at baseline, as well as at 0, 20, 40, 60, 90, and 120 min following TBS applications. During the session, the subjects will watch a muted video so that they stay alert during the whole experiment.

Each subject will have 4 visits.
1. MEP----iTBS50----MEP
2. MEP----iTBS30----MEP

3. MEP----cTBS50----MEP
4. MEP----cTBS30----MEP

Stimulation and Recording
Subjects will be seated in a comfortable chair for all procedures. Single-pulse TMS will be used to evoke MEPs from the right first dorsal interosseous FDI muscle target muscle. Electromyographic recordings will be made from the right FDI and abductor pollicis brevis (APB), which serves as a control muscle, using two Ag–AgCl surface electrodes arranged in a belly-tendon montage. Signals will be sampled at a rate of 5 kHz, amplified 1000 and filtered 20–1000 Hz before we store on a computer for offline analysis. Single-pulse TMS with monophasic waveform will be applied using a Magventure Magpro X100 magnetic stimulator Magventure, Farum, Denmark connected to a figure-of-eight magnetic coil. The optimal scalp site for evoking MEPs in the right FDI will be identified from M1 with the help of neuronavigation. The coil direction will be kept perpendicular to the nearest sulcus.

The mapping of the optimal location will be done with a supra threshold stimulation intensity evoking MEPs of around 1mV. After finding the optimal location, the coil will be rotated slightly in the tangential plane to check whether the induced electric field is optimal if not, the coil direction will be adjusted. At the optimal location, the rMT will be calculated with Motor threshold hunting paradigm, i.e. PEST. Thereafter, a baseline recruitment curve will be done 90 rMT-150 rMT, 10 pulses/intensity, interstimulus interval 5s and a cortical silent period threshold will be calculated with PEST.

rTMS Stimulation
rTMS will be applied using a Magventure Magpro. The rMT at the optimal cortical FDI representation will be calculated with the PEST. The intensity of TBS application will be 70-100 active or resting MT, as determined by investigator.

Theta-Burst Stimulation
TBS will be applied with a biphasic waveform using a Magventure Magpro Magventure, Farum, Denmark. The rMT at the optimal cortical FDI representation will be calculated with the PEST. The intensity of TBS application will be 80 of rMT.

TBS Paradigms
iTBS and cTBS will be applied with biphasic waveform using a Magventure Magpro Magventure, Farum, Denmark. Two cTBS and two iTBS paradigms with varying pulse configurations will be employed in this study. cTBS50 consists of a total of 600 stimuli applied in bursts of 3 stimuli at 20 ms intervals 50 Hz, with bursts repeated at 200ms intervals 5Hz. In the cTBS30 paradigm, bursts consisted of 3 stimuli applied at intervals of 33.3 ms 30 Hz, with bursts repeated at 167 ms intervals 6 Hz. As with the cTBS50 paradigm, cTBS30 will consist of a total of 600 stimuli. iTBS50, consists of a total of 600 stimuli applied in bursts of 3 stimuli at 20 ms intervals 50 Hz, with bursts repeated at 200ms intervals 5Hz and an 8 second intertrain interval between triplet. iTBS30 consists of bursts consisted of 3 stimuli applied at intervals of 33.3 ms 30 Hz, with bursts repeated at 167 ms intervals 6 Hz for three bursts then a 8 second intertrain interval. As with the iTBS50 paradigm, iTBS30 will consist of a total of 600 stimuli. The intensity of TBS

application will be set relative to resting motor threshold (RMT), measured using a biphasic pulse waveform with the rTMS coil. RMT will be defined as the minimum stimulus intensity sufficient to evoke MEPs in the right FDI at rest with peak-to-peak amplitudes of at least 50 lV in five of 10 consecutive trials. After TBS, MEP recruitment curves and cortical silent period thresholds will be recorded at 0, 20, 40, 60, 90, and 120 min following TBS applications.

EXPERIMENT 3: Optimal Intersession Interval
This experiment builds on previous understanding of the optimal intersession interval for spaced TBS which suggests that for cTBS, the optimal ISI is 15 minutes while with iTBS the optimal ISI is 30 minutes. We will utilize the burst frequency determined to be optimal from experiment 1. We will apply TBS over the left, dominant M1. TBS will be repeated two times separated by 15, 30, 45, or 60 min intersession interval. Subjects will attend eight sessions no <4 days apart, receiving the cTBSXX-15-cTBSXX, cTBSXX-30-cTBSXX, cTBSXX-45-cTBSXX, cTBSXX-60- cTBSXX, iTBSXX-15-iTBSXX, iTBSXX-30-iTBSXX, iTBSXX-45-iTBSXX, and iTBSXX-60-iTBSXX applied at 80 of RMT. The order in which they will receive each paradigm will be randomized between subjects. MEP recruitment curves and cortical silent period thresholds will be recorded at baseline, and at 0, 20, 40, 60, 90, and 120 min following the second TBS application.

Each subject will have 8 visits. 22 number of participants.
1. MEP----iTBSXX----15 min----iTBSXX----MEP
2. MEP----iTBSXX----30 min ----iTBSXX----MEP
3. MEP----iTBSXX----45 min ----iTBSXX----MEP
4. MEP----iTBSXX----60 min ----iTBSXX----MEP
5. MEP----cTBSXX----15 min ----cTBSXX----MEP
6. MEP----cTBSXX----30 min ----cTBSXX----MEP
7. MEP----cTBSXX----45 min ----cTBSXX----MEP
8. MEP----cTBSXX----60 min ----cTBSXX----MEP

XX=optimal burst frequency from experiment
Motor Evoked Potentials (MEPs)

Subjects will be seated in a comfortable chair for all procedures. Single-pulse TMS will be used to evoke MEPs from the right first dorsal interosseous (FDI) muscle. Electromyographic recordings will be made from the right FDI using two Ag– AgCl surface electrodes arranged in a belly-tendon montage. Signals will be sampled at a rate of 5 kHz, amplified ##1000 and filtered 20–1000 Hz before we store on a computer for offline analysis. Single-pulse TMS with monophasic waveform will be applied using a Magventure Magpro X100 magnetic stimulator Magventure, Farum, Denmark connected to a figure-of-eight magnetic coil external wing diameter, 90 mm . The coil will be held tangentially to the skull over the left M1, with the handle pointing 45? posterolaterally. The optimal scalp site for evoking MEPs in the right FDI will be identified and marked using a Watersoluble felt marker, and the intensity of stimulation will be adjusted to evoke baseline MEPs of approximately 1 mV amplitude measured peak-to peak.

TBS Paradigms

iTBS and cTBS will be applied with biphasic waveform using a Magventure Magpro Magventure, Farum, Denmark. One of two cTBS and two iTBS paradigms with varying pulse configurations will be employed in this study. cTBS50 consists of a total of 600 stimuli applied in bursts of 3 stimuli at 20 ms intervals 50 Hz, with bursts repeated at 200ms intervals 5Hz.

In the cTBS30 paradigm, bursts consisted of 3 stimuli applied at intervals of 33.3 ms 30 Hz, with bursts repeated at 167 ms intervals 6 Hz.

As with the cTBS50 paradigm, cTBS30 consists of a total of 600 stimuli. iTBS50, consists of a total of 600 stimuli applied in bursts of 3 stimuli at 20 ms intervals 50 Hz, with bursts repeated at 200ms intervals 5Hz and an 8 second intertrain interval between triplets. iTBS30 consists of bursts consisted of 3 stimuli applied at intervals of 33.3 ms 30 Hz, with bursts repeated at 167 ms intervals 6 Hz for three bursts then an 8 second intertrain interval.

In Experiment 1, the optimal burst frequency for both cTBS and iTBS will be determined and that optimal cTBS and
iTBS frequency will be utilized in this portion of the study.

EXPERIMENT 4: Neuroimaging
This experiment will form the bulk of the study and involves determining the rs fc MRI changes seen with spaced TBS, as well as determining how these rs fc MRI changes correlate with iTBS/cTBS response. Functional connectivity between pre-motor and motor cortex will be assessed. MRIs will be done at the Center for Cognitive and Neurobiological Imaging at Stanford University, or at the Richard Lucas Center for Imaging. All scans will be governed by each respective imaging center's safety protocols.

Resting state functional MRI and MR spectroscopy may be performed. The experimental procedures TBS applications of the fMRI sessions will be timed equivalent to the time 0 post spaced theta-burst stimulation of the MEP sessions from Experiment 2. In addition to the MEP acquisition, resting-state fMRI time series will be acquired at baseline and after the second application of cTBS and iTBS. Before the baseline fMRI measurements, the "hotspot" and RMT will be assessed using the neuronavigation setup.Subjects will attend two sessions no <4 days apart, receiving the cTBSXXYY-cTBSXX, and iTBSXX-YY-iTBSXX applied at 80 of RMT. The order in which they will receive each paradigm will be randomized between subjects. The fMRI sessions will start with a baseline resting-state scan duration 10 min where subjects will be instructed to lie motionless in the scanner with open eyes fixating a red cross, which was presented on a screen visible through a mirror attached to the MR head coil. After completion of the resting-state MRI, subjects will be asked to perform an active motor task, which will serve as a functional localizer for determining coordinates of M1 and other motor related regions for subsequent analyses.

This "activity" condition will be acquired after the resting state scan. After completion of the baseline fMRI session, subjects will be transported from the scanner to the anteroom of the MR console again sitting in the MR wheelchair without moving their right arm.

After coregistration with the neuronavigation system, spaced TBS will be applied separated by YY min controlled by a stopwatch. After the TBS, there will be another resting-state fMRI. The time protocol in the fMRI sessions will be identical to the one used in the MEP sessions.

Each subject will have 2 visits.
1. MRI-----iTBSXX----YY min----iTBSXX----MRI
2. MRI-----cTBSXX----YY min ----cTBSXX----MRI
XX=optimal burst frequency from experiment 1
YY=optimal intersession interval from experiment 2

Motor Evoked Potentials MEPs)
Subjects will be seated in a comfortable chair for all procedures. Single-pulse TMS will be used to evoke MEPs from the right first dorsal interosseous FDI muscle. Electromyographic recordings will be made from the right FDI using two Ag–AgCl surface electrodes arranged in a belly-tendon montage. Signals will be sampled at a rate of 5 kHz, amplified ##1000 and filtered 20–1000 Hz before we store on a computer for offline analysis.

Single-pulse TMS with monophasic waveform will be applied using a Magventure Magpro X100 magnetic stimulator Magventure, Farum, Denmark connected to a figure-of-eight magnetic coil external wing diameter, 90 mm. The coil will be held tangentially to the skull over the left M1, with the handle pointing 45 posterolaterally. The optimal scalp site for evoking MEPs in the right FDI will be identified and marked using a watersoluble felt marker, and the intensity of stimulation will be adjusted to evoke baseline MEPs of approximately 1 mV amplitude measured peak-to peak .

TBS Paradigms
iTBS and cTBS will be applied with biphasic waveform using a Magventure Magpro Magventure, Farum, Denmark. One of two cTBS and two iTBS paradigms with varying pulse configurations will be employed in this study. cTBS50 consists of a total of 600 stimuli applied in bursts of 3 stimuli at 20 ms intervals 50 Hz, with bursts repeated at 200ms intervals 5Hz.

In the cTBS30 paradigm, bursts consisted of 3 stimuli applied at intervals of 33.3 ms 30 Hz, with bursts repeated at 167 ms intervals 6 Hz. As with the cTBS50 paradigm, cTBS30 consists of a total of 600 stimuli. iTBS50, consists of a total of 600 stimuli applied in bursts of 3 stimuli at 20 ms intervals 50 Hz, with bursts repeated at 200ms intervals 5Hz and an 8 second intertrain interval between triplets. iTBS30 consists of bursts consisted of 3 stimuli applied at intervals of 33.3 ms 30 Hz, with bursts repeated at 167 ms intervals 6 Hz for three bursts then an 8 second intertrain interval. In Experiment 1, the optimal burst frequency for both cTBS and iTBS will be determined and that optimal cTBS and iTBS frequency will be utilized in this portion of the study.

EXPERIMENT 5: AFFECTIVE STATE
This experiment will investigate the effect of TMS-induced neuroplasticity on evoked-related potential ERP responses to emotional and neutral faces, and motor-evoked

potential MEP responses to motor cortex 1 stimulation, as measured by electroencephalogram EEG and electromyogram EMG, respectively. ERP and MEP measurements will be taken prior to and following thetaburst TMS.

Evoked Related Potentials (ERPs)
Subjects will be seated in a comfortable chair for all procedures. EEG recordings will be made while subjects view emotional and neutral faces displayed on a computer screen. Subjects will then undergo the iTBS or cTBS protocol
(see below). ERP and MEP responses will be measured again following TBS and compared to pre-TBS ERPs to measure the amount and valence of plasticity induced by TBS, and how this was modulated by the induced affective state.

Motor Evoked Potentials (MEPs)
Subjects will be seated in a comfortable chair for all procedures. Single-pulse TMS will be used to evoke MEPs from the right first dorsal interosseous (FDI) muscle. Electromyographic recordings will be made from the right FDI using two Ag–AgCl surface electrodes arranged in a belly-tendon montage. Signals will be sampled at a rate of 5 kHz, amplified ##1000 and filtered 20–1000 Hz before we store on a computer for offline analysis. Single-pulse TMS with monophasic waveform will be applied using a Magventure Magpro X100 magnetic stimulator Magventure, Farum, Denmark connected to a figure-of-eight magnetic coil external wing diameter, 90 mm. The coil will be held tangentially to the skull over the left M1, with the handle pointing 45 posterolaterally. The optimal scalp site for evoking MEPs in the right FDI will be identified and marked using a watersoluble felt marker, and the intensity of stimulation will be adjusted to evoke baseline MEPs of approximately 1 mV amplitude measured peak-to peak.

TBS Paradigms
iTBS and cTBS will be applied with biphasic waveform using a Magventure Magpro Magventure, Farum, Denmark. One of two cTBS and two iTBS paradigms with varying pulse configurations will be employed in this study. cTBS50 consists of a total of 600 stimuli applied in bursts of 3 stimuli at 20 ms intervals 50 Hz, with bursts repeated at 200ms intervals 5Hz. In the cTBS30 paradigm, bursts consisted of 3 stimuli applied at intervals of 33.3 ms 30 Hz, with bursts repeated at 167 ms intervals 6 Hz.

As with the cTBS50 paradigm, cTBS30 consists of a total of 600 stimuli. iTBS50, consists of a total of 600 stimuli applied in bursts of 3 stimuli at 20 ms intervals 50 Hz, with bursts repeated at 200ms intervals 5Hz and an 8 second intertrain interval between triplets. iTBS30 consists of bursts consisted of 3 stimuli applied at intervals of 33.3 ms 30 Hz, with bursts repeated at 167 ms intervals 6 Hz for three bursts then an 8 second intertrain interval.

In Experiment 1, the optimal burst frequency for both cTBS and iTBS will be determined and that optimal cTBS and iTBS frequency will be utilized in this portion of the study. Subjects will view movie clips tailored to induce primary affective states during the iTBS or cTBS protocol targeted to either dlPFC or area M1.

TMS-EEG
TMS-EEG recordings may be collected at various points throughout the study. During TMS-EEG recordings, subjects will be instructed to listen to white noise.

BIOMARKERS
Cortisol and other biomarkers may be collected at points during the study.

OTHER TASKS/QUESTIONNAIRES:
Participants will be asked to perform the critical feedback task CFT at various points in the study. This is a simple computer-based question and answer task that asks the participant to perform mental math and provides them with accurate or bogus feedback on their performance.

- Hamilton rating scale for depression (HAMD)
-Montgomery–Asberg Depression Rating Scale
- Beck depression inventory
- Inventory of depressive symptoms
- Other mood questionnaires
- Emotion Induction task
- Emotional identification task

Video Recording
-Video recordings will be conducted during clinical assessments and interviews for participants who consent to video recordings. More details are indicated in section 2d.

b. Procedure Risks

These methods are the least risky because the intervals of treatment have been shown to be appropriate for theta burst stimulation in the motor system with no adverse outcomes.

c. Use of Deception in the Study

No deception will be used.

d. Use of Audio and Video Recordings

We will offer study participants the option of videotaping the clinical assessments conducted with them while enrolled in the study. They will have to sign a separate consent for this to occur. The video recordings will be recorded using Zoom video from an encrypted Stanford owned laptop. The recordings will be available for training purposes for study personnel only. We will not use or distribute the videos to outside personnel or scientific meetings etc. unless directly indicated by the participant on the video consent form attached in section 13.

e. Alternative Procedures or Courses of Treatment

N/A

f. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

N/A

g. Study Endpoint(s)

Because this is a mechanistic study and not a clinical trial, the primary endpoint is an assessment of the duration of effect of an application of TBS. We will assess the findings of the trial after all subjects have been run. We will not be performing interim analysis as this is not a treatment study and the risks of the TMS intervention are either minor or very rare.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

Theta-Burst Stimulation
There is early indication that utilizing TBS, which mimics natural brain rhythms, is an effective stimulation method for modulation of human cortex Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005. While first utilized in the motor cortex, TBS has been since utilized in the limbic and cognitive areas with some early success in treating depression Chung, Hoy, & Fitzgerald, 2015. The benefits of this form of stimulation is that it appears to allow for a reduction in the time of treatment while maintaining a similar efficacy to traditional 40 min 10Hz rTMS stimulation in an early comparison study Bakker et al., 2015. Stimulation of the primary motor cortex M1 specifically, can influence both motor output and pain perception in both healthy and chronic pain populations Zaghi et al., 2010; Sacco et al., 2014. Associated changes in brain activity can be detected using functional magnetic resonance imaging MRI methods. There is emerging evidence from the motor system that the spacing or timing between theta burst trains is important in long-term potentiation/depression LTP/LTD. If the train goes on for two long without a necessary time interval, there is a reversal of the initial direction LTP or LTD Gamboa, Antal, Moliadze, & Paulus, 2010.

TBS Burst frequency
Originally, the TBS burst frequency was determined to be 50Hz at 5Hz intervals. Recently, a modified version of the inhibitory form of TBS continuous---cTBS was demonstrated to produce more consistent suppression of the motor evoked potential MEP than the traditional form of cTBS. This modified form has been used in treatment applications with success. For the excitatory form of TBS intermittent---iTBS, iTBS30 has demonstrated a similar change in the MEP as iTBS50. Modifications to the burst frequency have been described to potentially affect clinical outcome in TBS for MDD. While single experiments have been performed demonstrating differences between TBS30 and TBS50, there has yet to be a study comparing iTBS and cTBS in the same participants between these two burst frequency conditions.

Spaced Theta-Burst Stimulation
Spaced theta-burst stimulation (sTBS) is a patterned application of TBS that was studied initially in animal models. It has been demonstrated that en masse stimulation with TBS

produces effects that are opposite to the intended effect. Spaced, patterned theta-burst is therefore required. sTBS was assessed in healthy controls with MEP change and it has been demonstrated that RMT70 produces 2 hours of suppression of the MEP which is affected by preceding hand activation. This approach has been assessed for saccade induction with non-linear increases in saccades. Recently, the technique has been applied to disease conditions such as hemispatial neglect and depression.

Intersession Interval of Spaced TBS
The optimal ISI is unknown for iTBS and cTBS. It appears that 15 minutes as has previously used by one group for depression, may be too short for late stage LTP induction in the case of iTBS. For cTBS, 10-15 min has been most regularly used, but longer ISI have yet to be explored.

TBS-induced Change to Resting State Functional Connectivity
It has been demonstrated that rTMS and more specifically TBS are functional connectivity (fc) modulators that are stimulation parameter specific (excitatory or inhibitory). Furthermore, it has been demonstrated that patterned TBS application produces changes in fc MRI that are correlated with changes in MEP. It has been demonstrated that optimized ISI can produce an optimized change in the fc. Furthermore, it has been demonstrated that relative amounts of fc within the targeted neural network is correlated with change or no change in the fc and change or no change in the MEP. This property has been reflected in treatment application as well.

TBS-induced Change to IL TMS-fMRI
IL TMS-BOLD has been demonstrated to reflect inherent network properties of the TMS targeted neural network. It has been demonstrated that pharmacology or TBS can changes these properties as reflected by the differential BOLD activation. One group has demonstrated that TBS to a targeted neural network can change the BOLD activation after IL TMS-BOLD as compared to pre TBS IL TMS-BOLD.

b. Findings from Past Animal Experiments

None

4. DEVICES USED IN THE STUDY

a. Investigational Devices (Including Commercial Devices Used Off-Label)

Investigational Device 1	
Name:	MagPro X100
Description:	Transcranial Magnetic Stimulation Device with theta burst stimulation
Significant Risk? (Y/N)	N
Rationale for Non-Significant Risk	The 'traditional 10Hz TMS' is on label and the theta burst stimulation is off label. It is the same device for both. The Magventure is about to be approved by the FDA for depression in 2 weeks. When that happens, the 'traditional 10Hz' stimulation will be on label with an approved device.The theta burst stimulation is minimal risk because the risk of seizure is very low only reported once in literature and there is no other risk other than minimal scalp irritation. We will be using an approved device 'off label' stimulation parameters which has a lower risk profile than the on label approved parameters.
Investigational Device 2	

Investigational Device 1	
Name:	MRI-safe infrared diode laser stimulator
Description:	MRI-safe infrared diode laser stimulator
Significant Risk? (Y/N)	N
Rationale for Non-Significant Risk	Does not fulfill the definition of a significant risk device.
Investigational Device 3	
Name:	NextStim
Description:	NextStim TMS device
Significant Risk? (Y/N)	N
Rationale for Non-Significant Risk	NextStim is an FDA-approved TMS device for treatment of depression

5. PARTICIPANT POPULATION

a. Planned Enrollment

we will recruit 60 healthy participants only at Stanford-affiliated sites

b. Age, Gender, and Ethnic Background

Participants will be 18-80 year-old right handed male and female subjects with no history of psychiatric or neurological diagnoses and no current use of psychoactive medications. They will be recruited to participate in this study, all of whom will be blinded to the purpose of the study. All subjects will be screened for any contraindications to TMS (23) and will give their informed written consent prior to participation. This study is approved by the Stanford University Institutional Review Board and performed in accordance with the Declaration of Helsinki

c. Vulnerable Populations

We will not include children, pregnant women, decisionally impaired. We will include economically/educationally disadvantaged and homeless. We will also include employees and students rTMS is a low-risk procedure, but we will ensure all safety measures are taken for these participants.

d. Rationale for Exclusion of Certain Populations

Women and minorities are included. Children are not because they are typically excluded from rTMS studies.

e. Stanford Populations

Employees, students and lab personnel may sign up for this study in compliance HIPAA policy.

f. Healthy Volunteers

All participants are healthy volunteers.

g. Recruitment Details

We intend to recruit 30 healthy subjects. We will obtain IRB approval for flyers advertising the study.

We will be utilizing social media to reach potential participants. We have a Facebook page for our research group that we will use to promote the study. We will do so using only IRB approved language.

We will also begin utilizing the Stanford Research Registry (protocol 25422) to recruit study participants. The research registry is a list of individuals who have consented to be contacted by research at Stanford and at present includes over 1,000 volunteers.

h. Eligibility Criteria

i. Inclusion Criteria

1. Age 18-80 years old
2. Right-handed
3. Agree to having fMRI scan
4. Willingness to suspend use of analgesic drugs or cough suppressants for 24 hours prior to the scans
5. Proficiency in English sufficient to complete questionnaires/follow instructions during fMRI assessments
6. US Citizen or resident able to receive payment legally

ii. Exclusion Criteria

1. A medical condition that would contraindicate the use of rTMS
2. Any condition that would contraindicate MRI (like ferromagnetic metal in the body)
3. Pregnancy or breast feeding
4. Any significant neurologic disease, including dementia, multi-infarct dementia, Parkinson's or Huntington's disease, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, history of significant head trauma.
5. Current antidepressant use (must be washed out for two weeks prior to starting protocol).
6. Inability to stop taking medication contraindicated with treatment.
7. Motor threshold is unable to attained.

i. Screening Procedures

The principal investigator (PI) and/or study staff will:

1. Obtain signed informed consent from the potential participant before any study-specific procedures are performed.
2. Assign potential participant a unique enrollment number.
3. Determine participant eligibility.

j. Participation in Multiple Protocols

We will not enroll participants that are involved in any other treatment trial. We will coordinate with any ongoing biomarker studies to ensure that the treatment follows the

biomarker study. The consent form clearly asks patients if they are participating in any other studies. The PI and/or research coordinator will also ask the patient.

k. Payments to Participants

Participants will be paid $25 per visit.

Added 30 additional health controls who will undergo an MRI scan, without use of rTMS or TBS. These participants will be compensated a total of $150 USD for their participation in the study.

l. Costs to Participants

None.

m. Planned Duration of the Study

This research study is expected to take approximately 8 months to complete with 4 days of active participation by each participant.

6. RISKS

a. Potential Risks

i. Investigational devices

N/A

ii. Investigational drugs

N/A

iii. Commercially available drugs, biologics, reagents or chemicals

N/A

iv. Procedures

Receiving rTMS may cause minor discomfort at the site of stimulation, occurring only during the time of stimulation.

Participants may experience a localized twitching sensation due to the magnetic field changes during the MRI scan. This should not be painful.

v. Radioisotopes/radiation-producing machines

N/A

vi. Physical well-being

Participants will have all measures exerted to reduce the chances of seizure and discomfort from stimulation of rTMS. Receiving rTMS may cause minor discomfort at the site of stimulation, occurring only during the time of stimulation.

Participants may experience a localized twitching sensation due to the magnetic field changes during the MRI scan. This should not be painful.

vii. Psychological well-being

Participants will be placed in a relaxing environment to help reduce any psychological well being.

Patients may find the study visits to be inconvenient.

viii. Economic well-being

Study should not effect economic well-being.

ix. Social well-being

No risk to social well-being is anticipated.

x. Overall evaluation of risk

Low – innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device.

b. Procedures to Minimize Risk

We will have a trained rTMS treater in the room at all times monitoring for changes in level of consciousness. We will eliminate any offending agents that may increase risk of seizure. The protocol directors will monitor all physiological data obtained for adverse effects. A physician (Dr. Nolan Williams, Dr. Spiegel, or medical backup) will be in the building and on call in case of any seizures or other adverse events.

If suicidal tendencies are indicated during completion of the MINI, the participant will be evaluated in more detailed by Dr. Nolan Williams or Dr. David Spiegel who are both trained psychiatrists. They will decide on the best course of action or treatment to ensure the participant's safety.

c. Study Conclusion

The experiment will terminate when the final participant has completed their treatment and all data has been analyzed.

d. Data Safety Monitoring Plan (DSMC)

i. Data and/or events subject to review

The study's data and safety monitor will be the Protocol Director. In addition, participants can always call with questions or concerns. Serious Adverse Events, if any, will be reported ot the Protocol Director within 24 hours and to the FDA within 48 hours. An events that occur will be reported to the IRB per the prompt reporting guidelines.

ii. Person(s) responsible for Data and Safety Monitoring

The Protocol Director will perform this function.

iii. Frequency of DSMB meetings

The Protocol Director will perform this function.

iv. Specific triggers or stopping rules

We will report all SAE.

v. DSMB Reporting

Monthly

vi. Will the Protocol Director be the only monitoring entity? (Y/N)

Yes

vii. Will a board, committee, or safety monitor be responsible for study monitoring? (Y/N)

No

7. BENEFITS

Participants will most likely not benefit from this study. Understanding the duration of effect of this new type of rTMS treatment will serve as necessary knowledge for designing future TBS treatment studies.

8. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.