

Closed-loop Optimized rTMS for Depression

Study Protocol with Statistical Analysis Plan and Informed Consent Form

NCT04142320
December 14, 2020

SPECIFIC AIMS

Research Objectives: We are in critical need of targeted and individualized treatments for mental health disorders, which affect nearly 50% of Americans during our lifetimes¹. Brain stimulation treatments, including repetitive transcranial magnetic stimulation (rTMS), represent the front-line of innovative approaches to correct dysfunctional brain networks for patients suffering from mental illness². rTMS is FDA-approved for depression and OCD with clinical trials underway for PTSD and substance use, among others. However, as currently administered, rTMS lacks a biomarker to individually direct and optimize treatment and thus suffers from a poor clinical response rate (<50%³⁻⁵). Without personalization of rTMS, we risk a one-size-fits-all treatment for all psychiatric disorders, not dissimilar to how antidepressants are administered.

During residency, I **identified a depression severity biomarker** from a double-blind randomized clinical trial treating depressed patients with one month of active or placebo rTMS. I evaluated changes using a causal brain mapping tool combining TMS and electroencephalography (TMS-EEG), from which I co-developed the first automated artifact rejection algorithm⁶ and established test-retest reliability⁷. The 'p30' TMS-EEG signal arises 30ms after a single TMS pulse in the fronto-parietal network (FPN), a region implicated in depression⁸⁻¹⁰. We found that FPN p30 suppression significantly predicted clinical improvement to rTMS. This work, currently under review, represents the first brain biomarker from a placebo-controlled clinical trial for rTMS. Direct brain recordings further suggest that a single stimulation session is sufficient to suppress the p30¹¹, indicating that **FPN p30 can be monitored daily to support empiric treatment optimization**. As such, I aim to develop the **first broadly generalizable platform for real-time biomarker monitoring (Aim #1) and personalized rTMS treatment (Aims #2 & 3)**. I will enroll 54 depressed patients to participate in a cross-over, placebo-controlled study directly comparing personalized, closed-loop rTMS to standard rTMS. I propose three main aims:

Aim 1: To create a real-time platform for monitoring FPN p30 changes (depression severity biomarker). I will focus on p30 suppression and include the capability to monitor other relevant EEG features. Real-time biomarker monitoring is a necessary step for closed-loop interventions.

Aim 2: To identify the stimulation parameters that causally and maximally suppress the p30. *Aim 2.1:* I will determine the clinically-utilized rTMS pattern that elicits the strongest p30 suppression. *Aim 2.2:* I will then fine-tune stimulation parameters (power, duration, frequency) in an event-related design and measure the degree of p30 suppression. Precise delineation of this causal relationship between stimulation and biomarker engagement is critical for computational modeling.

Aim 3: To test whether closed-loop rTMS more strongly suppresses the p30 compared to standard rTMS. *Aim 3.1:* I will build an individualized model using *neural networks* that maps stimulation patterns to p30 changes. I will then invert this model using *Bayesian machine learning* to determine the pattern that maximally suppresses the p30. *Aim 3.2:* I will update this pattern in real-time using *control systems* and directly compare this approach to standard rTMS in depressed patients. This will yield a closed-loop treatment based on empiric biomarkers that more effectively modulates an individual's brain circuitry and potentially improves clinical outcomes.

Successful implementation of this work includes the early stratification of treatment responders and personalized and more effective treatments for non-responders. This approach is broadly applicable to other depression biomarkers, all psychiatric populations treated with rTMS, and other brain stimulation modalities.

Institutional Support: The department has dedicated significant laboratory space and \$100,000/year for two years for my independent research. I will be an Instructor in the Major Laboratories and Clinical and Translational Neurosciences Incubator and report directly to the department chair. The department is committed to and actively engaged in securing a tenure-track Assistant Professor position for me.

Early Independence Rationale: My strong background spanning clinical and research disciplines make me well-suited to transition early to independence. I published 20+ journal articles (13 first-author), wrote two book chapters, delivered 10+ invited lectures, (5+ internationally), mentored 8 students (two with first-author publications under my supervision), been awarded multiple grants including an F31 and a pending K23 (fundable score), generated two patents, and oversee two large clinical trials involving 50+ personnel. I have established collaborations and am drafting grants with neurologists (Josef Parvizi), neurosurgeons (Casey Halpern), and neuroscientists (Rob Malenka, Karl Deisseroth) at Stanford. I have discussed independence at length with my mentor, Amit Etkin. In contrast to others who focus on *increasing access to treatment* or *identifying group-level neuroimaging biomarkers*, I will focus on mechanism, first principles, and engineering techniques to create *trans-diagnostic platforms for real-time biomarker monitoring and individualized treatment optimization*. I hope to establish the fundamental principles of human brain plasticity and platforms for rapid biomarker development, engagement, and integration into personalized brain stimulation treatments.

VI. Research challenge

A1. The need for personalized brain stimulation. Nearly 50% of all Americans will suffer from a mental health disorder during our lifetimes¹. Depression alone is the leading cause of disability worldwide (Fig 1)²⁶. Medications are currently ineffective or not tolerated for more than a third of depressed patients (5.3 million patients in the US)²⁷, fueling the need for alternative treatments. Non-pharmacologic FDA-approved brain stimulation treatments for depression include electro-convulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS). These interventions attempt to normalize dysfunctional brain circuits associated with depression and other psychiatric disorders². ECT is clinically effective (50-80% response rate²⁸), but requires general anesthesia, has significant stigma and side effects, and cannot be implemented in outpatient clinics. In contrast, rTMS is an outpatient procedure with minimal stigma or side effects. rTMS uses strong (1-2T) focused magnetic fields to induce electrical currents in neural tissue and elicit neuronal firing²⁹. When applied repetitively, rTMS can strengthen or weaken brain excitability³⁰. Current response rate of rTMS for depression is <50%³⁻⁵. However, conventional methodology does not take into account significant heterogeneity between patients³¹ and is currently applied in a manner that is one-size-fits-all (without any individual optimization of the stimulation pattern) and open-loop (with no measurement or adjustment during rTMS). To personalize brain stimulation, we must (1) measure and monitor brain changes in real time; (2) determine the optimal stimulation patterns to maximize brain changes; (3) and develop adaptive treatments to drive desired changes on an individual patient-specific level.

A2. Closing the loop. The great potential of brain stimulation treatment is to selectively modulate brain networks by adjusting stimulation based on a patient's brain structure, function, and symptoms. A 'closed-loop' approach to stimulation (Fig 2) accomplishes this by measuring brain activity and continuously adjusting the stimulation parameters to maximize circuit change. Although closed-loop systems are standard in robotics, heating/cooling systems, and autonomous vehicle control, closed-loop brain stimulation is not used for treatment of any brain disorder, with the exception of certain implantable devices to treat epilepsy³². Closed-loop systems pairing stimulation and measurement of electrical brain activity have been shown to improve emotion regulation in preclinical rodent models^{33,34}, improve memory encoding using implanted electrodes in humans³⁵, and enhance neuronal synchronization using rTMS³⁶. The field is therefore well positioned to build on years of engineering refinement and neuroscientific progress to develop next generation closed-loop brain stimulation treatments.

A3. Causal probing of human brain networks. While many non-invasive neuroscience tools measure associations between brain regions (e.g., functional MRI, resting EEG), understanding the causal influence of one region on another remains a challenge. I plan to measure causal brain changes using TMS paired with electroencephalography (TMS-EEG, see terminology insert), a non-invasive technique that can be standardized and easily adapted to clinical use. TMS-EEG perturbs brain circuits and measures the brain's response with millisecond resolution, sufficient to capture *brain plasticity*, a change in the synaptic strength of neurons. TMS-Evoked Potentials (TEPs)³⁷⁻⁴⁰ are the EEG response phase-locked to the TMS pulse. TEPs have been used to monitor consciousness⁴¹, study sleep^{39,42}, identify brain signatures of mental disorders^{43,44}, and track brain changes after ECT⁴⁵. Typical TEPs (Fig 2B) consist of an early potential (<15ms, often difficult to resolve

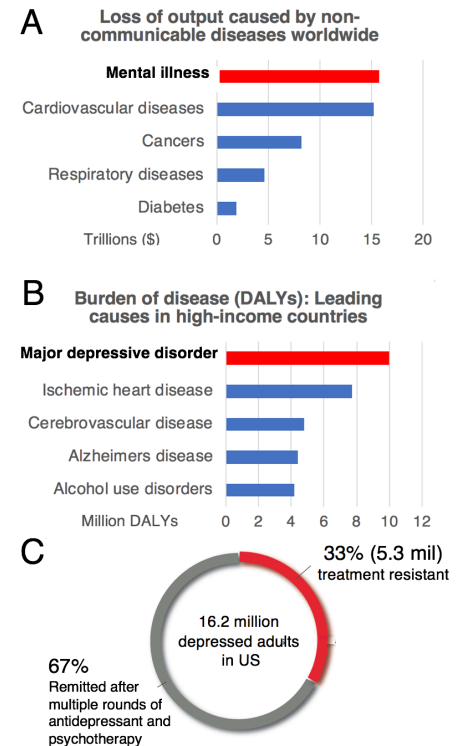
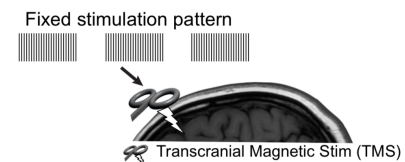


Figure 1 – The devastating burden of mental illness and treatment-resistant depression.

A. Open-loop rTMS



B. Closed-loop rTMS

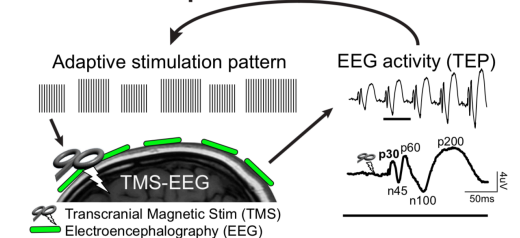


Figure 2 - Illustration of open-loop and adaptive closed-loop rTMS approaches. A) Standard 'open-loop' 10Hz rTMS stimulates a target structure at fixed stimulation (power, frequency, duration). B) Adaptive 'closed-loop' rTMS uses online TMS Evoked Potentials (TEPs) to modify stimulation parameters to more effectively alter brain circuits. Insert: This project focuses on the 'p30' of the TEP, the voltage increase 30ms after a TMS pulse.

Typical TEPs (Fig 2B) consist of an early potential (<15ms, often difficult to resolve

due to low signal quality) that likely reflects increased spiking activity in pyramidal neurons^{29,46}, followed by later potentials (>15ms) that likely reflect decreased pyramidal neuron activity and increased interneuron activity⁴⁶⁻⁵⁰. To increase processing speed and reliability of TEPs, I co-developed and validated the first artifact rejection algorithm⁶ that automatically removes non-neural components (e.g., pulse artifact, muscle twitches, blinking³⁷⁻⁴⁰) from the TEP (see section C10 for details). I also demonstrated high test-retest reliability of TEPs across sessions⁷. In summary, TMS-EEG is a well-validated tool and ideally suited for the causal measurement of TMS-induced brain changes.

B1. Preliminary evidence for a brain biomarker in depression.

I recently completed a double-blind randomized clinical trial (NCT01829165) treating depressed patients with four weeks of daily 10Hz rTMS (typical treatment frequency and duration) or sham (no TMS) to the left prefrontal cortex. TEPs were measured before and after the month of rTMS treatment. I identified a *depression severity biomarker*, a positive voltage increase 30ms after a single TMS pulse (termed the 'p30'). rTMS treatment suppressed the p30 in the left fronto-parietal network (FPN), a region implicated in depression⁸⁻¹⁰ (Fig 3A-C). The degree of post-rTMS p30 suppression in the FPN importantly predicted over 50% of clinical response (Fig 3D, under review at the American Journal of Psychiatry).

In contrast to non-invasive studies, human intracranial recordings have greater spatial and temporal resolution with fewer artifacts and thus can provide insight to non-invasive findings. To mimic standard rTMS, I applied 15 minutes of 10Hz prefrontal intracranial electrical stimulation (5s on, 10s off, bipolar stimulation directly above layer 1 of the neocortex) and recorded the p30 of the electrically-induced evoked potential. Similar to rTMS, intracranial stimulation suppressed the FPN p30 for ~20 minutes (Fig 4A,B, recently published in the Journal of Neuroscience¹⁴). Regions that exhibited pre/post p30 changes could be predicted based on baseline connectivity (anatomical distance from stimulation site + pre-stimulation single pulse p30 amplitude). In summary, FPN p30 suppression predicted clinical outcome after rTMS treatment (Fig 3) and was observed in a predictable manner after a single stimulation session (Fig 4).

B2. Cortical inhibition as a proposed mechanism of the clinical effects of rTMS. There is a long-standing theory that 10Hz rTMS is efficacious by increasing the responsiveness of excitatory pyramidal neurons⁵¹. In contrast, more recent animal work has shown that 10Hz rTMS decreased both inhibitory synapse functioning⁵² and inhibitory activity during visual processing⁴⁶. Thus, 10Hz rTMS may instead increase net excitability by *decreasing cortical inhibition*, though these results have not been replicated in human patients, leaving the mechanistic basis of rTMS unclear. Our preliminary results support this claim. The p30 has been shown in animals⁵³ and humans⁵⁰ to be inhibitory in nature and I observed a decrease in p30 after 10Hz rTMS. Thus, 10Hz rTMS may exert its antidepressant effect by decreasing cortical inhibition in the fronto-parietal network.

B3. Current scientific challenge. While p30 suppression after rTMS relates to clinical outcome and may reflect a decrease in cortical inhibition, critically lacking is (1) a mechanistic understanding of how standard rTMS induces brain changes *during stimulation*; (2) development of stimulation patterns that *maximize this biomarker change*; and (3) demonstration of whether *closed-loop stimulation* is more effective at generating clinically-relevant brain changes. The goal of this award is thus to translate these findings across modalities (invasive to non-invasive), time (pre/post rTMS to real-time), and space

Key Definitions

TEP – TMS-Evoked Potential. The immediate effect of TMS on the EEG signal, derived using concurrent TMS-EEG. Components of the TEP include the 'p30,' a positive voltage increase 30ms after the TMS pulse.

pre/post p30 change – TEP changes *before and after rTMS sessions*, derived from single pulse TMS to evaluate brain changes.

intra-stimulation p30 changes – TEP changes recorded *during rTMS*.

stimulation train – a set of stimulation pulses grouped together

TMS plasticity – ability of the brain to change, here indexed by *change in p30 amplitude*

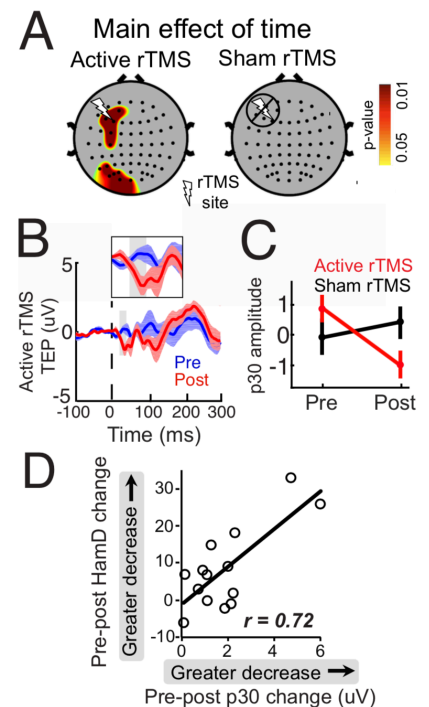


Figure 3 - Daily active 10Hz rTMS treatment suppresses the p30. Four weeks of rTMS treatment modulated the p30 but not other TEP components. A) Scalp topographic plot of the main effect of time (pre/post rTMS) in the p30 after cluster correction. B) TEP time series for the frontal cluster in A. Shaded vertical bar represents the p30. Insert shows 0-50ms of the TEP. C) Extractions of p30 from the frontal cluster. D) Correlation between p30 change in the frontal cluster and change in depressive symptoms (Hamilton depression scale, HamD). The degree of p30 change correlates with the degree of symptom improvement.

(laboratory to clinical settings) to develop a real-time brain plasticity monitoring system directing individualized and effective closed-loop treatments. Tools to quantitatively monitor brain changes in real-time have not been published or reported, even in the more technologically-advanced neurological or neurosurgical centers. If we wish to shift to a personalized approach, a tool with this capability is critical. Analogous to an anesthesiologist adjusting medications based on continuous heart rate and blood pressure readings, this brain monitoring tool will be integral for providers to adjust treatment parameters and maximize brain and clinical response.

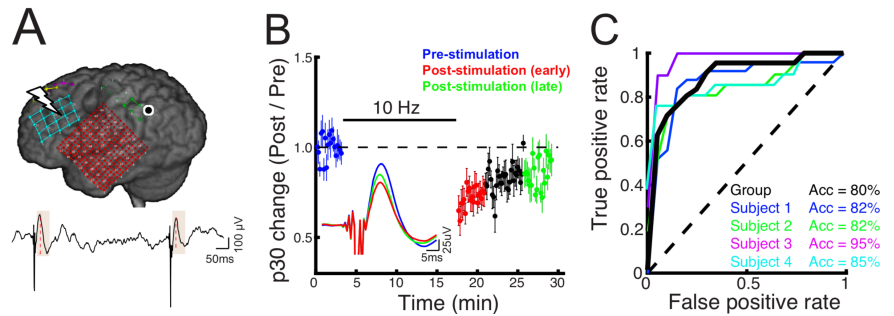


Figure 4 – Open-loop 10Hz intracranial repetitive stimulation suppresses the p30 in the fronto-parietal network in a predictable manner. A) Example of intracranial electrodes, stimulation site (lightning bolt), recording site (black electrode), and single trial evoked potential showing the p30 response. B) Change in p30 response after 10Hz stimulation. Insert: p30 waveform before and after stimulation. C) Receiver operating curves (ROC) demonstrating accuracy of predicting pre/post p30 change from baseline connectivity (anatomical distance from stimulation site + pre-stimulation single pulse p30 amplitude).

I hypothesize that the strength of brain changes (p30 suppression) induced in the targeted region (fronto-parietal network) during stimulation will predict clinical outcome, and closed-loop interventions that maximize this change will lead to enhanced therapeutic efficacy. By developing a platform for monitoring brain changes *during* stimulation (Aim #1) and mapping stimulation parameters to brain changes (Aim #2), I will build closed-loop treatments individualized to person and targeted network (Aim #3). Successful outcome of this proposal will result in early stratification of standard rTMS treatment responders and more effective and personalized interventions for treatment non-responders.

VII. Innovation. Brain stimulation represents an exciting alternative to medication that targets specific brain networks, but there has been minimal change in clinical rTMS since its FDA-approval for depression more than 10 years ago. Now with a recent approval for OCD (August 2018) and multiple phase III rTMS clinical trials underway for bipolar disorder, substance use disorders, and PTSD, without intervention we risk a one-size-fits-all treatment for all psychiatric disorders, not dissimilar to the trial-and-error nature of how antidepressants are administered (often based on side effect profile). We have developed a causal brain mapping technique (TMS-EEG) and identified a depression severity biomarker that can be monitored in the clinic. With high-density EEG we can identify brain sources from electrical activity observed on the scalp⁵⁴. Imaging studies have identified brain regions involved in depression⁸⁻¹⁰. Finally, machine learning is being integrated into diagnosis and treatment considerations in medicine (e.g., NCT02963441 for retinopathy, NCT03128268 for cardiology). For these reasons, we stand at a **critical intersection in mental health treatment**, transitioning from the non-specific and trial-and-error nature of past treatment approaches to neuroscientifically-informed targeted interventions. The work I propose here has the potential to transform brain stimulation to the forefront of personalized medicine⁵⁵⁻⁵⁷, where an patient's brain is used to develop circuit-informed individualized treatments. Importantly, we can also reduce mental health stigma by identifying brain regions that contribute to psychiatric disorders and targeting interventions to normalize these regions.

Besides its overarching novelty, this approach outlined in this proposal has several unique characteristics:

1) **A mechanistic understanding of human brain plasticity.** Studies typically only examine brain changes following rTMS through correlative neuroimaging⁵⁸⁻⁶¹. This approach yields a relatively simplistic description of rTMS changes with a measure that has a complex biological basis^{22,62-64} and cannot be sampled on a fast-enough timescale to adapt treatment. In contrast, using TMS-EEG we can examine the **causal** brain dynamics **following** rTMS, which I have shown to track depressive symptoms (Keller et al., under review). Here, I will for the first time develop a platform to monitor **brain plasticity** in real-time **during** rTMS, both during a single treatment session (~15-30 minutes) and across treatment days. This mechanistic characterization is critical to understand the underlying biology of human brain plasticity.

2) **A personalized, adaptive approach to brain stimulation.** Identifying a depression severity biomarker can support treatment stratification, helping predict responders and non-responders to rTMS. It can also be used for biomarker-driven treatment optimization, that can provide effective treatment for those non-responsive to standard treatment. This work represents a first in psychiatry to monitor a biomarker in real-time and continuously

optimize individual treatment based on this biomarker. It is worth noting that while closed-loop treatments have recently been implemented to stop seizures³² or minimize on-time for deep brain stimulators⁶⁵, to our knowledge this study represents the first to optimize treatment in real-time based on *maximizing an individual's brain change*. If successful, this work could spur other fields to similarly focus on maximizing plasticity to better treat symptoms. Finally, this platform is broadly applicable to other depression biomarkers, all psychiatric populations treated with rTMS, and other brain stimulation modalities (e.g. vagus nerve stimulation, deep brain stimulation).

VIII. Approach

C1. Aim 1: To create a real-time platform for monitoring FPN p30 changes (depression severity biomarker).

Rationale and significance: Typical studies examine brain changes following an entire treatment (up to a month) and relate these changes to clinical outcome. These studies critically miss the rich brain dynamics that occur during the stimulation period (*intra-stimulation*), where *brain plasticity* is initiated. How and where plasticity is initiated during stimulation is essential as it underlies the basis of rTMS treatment⁶⁶. To increase our mechanistic understanding and build the foundation for closed-loop treatment, I will develop the first clinic-ready platform to monitor real-time brain dynamics.

Preliminary Data: I demonstrated that 10Hz intracranial electrical stimulation, patterned to mimic rTMS, suppressed the p30, and the baseline connectivity profile predicted the degree of p30 suppression in all eight patients (Fig 4)¹⁴. Recently I explored how these *pre/post stimulation* changes relate to *intra-stimulation* dynamics. One can observe the rich intra-stimulation p30 dynamics induced by 10Hz stimulation (Fig 5A-C). As

stimulation progresses (later trains), prefrontal regions (#1) exhibited a temporal latency shift, such that it takes more pulses in a train to elicit a strong p30 response (dotted line). This change is not present in the parietal recording (#2). Additionally, as stimulation progresses, p30 effects in the FPN late in the train become apparent around train 20 (arcs at #1,2). Many regions exhibited no p30 change during stimulation (#3). There was a tight spatial correlation between intra-stimulation and pre/post p30 changes (Fig 5D, E). Although spatially similar, how these different components of intra-stimulation dynamics (increased p30 latency at dotted line, later p30 increase at arc) directly relate to lasting electrophysiological and clinical effects will be the focus of future investigation. Together, these findings suggest that real-time monitoring will enhance our understanding of how stimulation affects short- and long-term dynamics.

Overview of methods: Work thus far has identified a *depression severity biomarker* that (1) invasively can be monitored *during* stimulation¹¹, and (2) non-invasively predicted clinical improvement to rTMS treatment²⁰. These findings support the feasibility of **non-invasive real-time brain monitoring**. To implement, miniaturized low power amplifiers will quickly acquire data from 64-channel EEG sensors (Fig 6A). Next, automated artifact rejection algorithms²⁰ will identify the spatial filter to remove non-neural noise from pre-stimulation EEG data (Fig 6B). This spatial filter will be applied to clean incoming rTMS data for quantification with minimal delay (Fig 6C) and plotted in an intuitive Graphical User Interface (GUI, Fig 6D). I will quantify source localized maps of (1) p30 amplitude after each stimulation pulse; (2) p30 change during each stimulation train; and (3) the time frequency

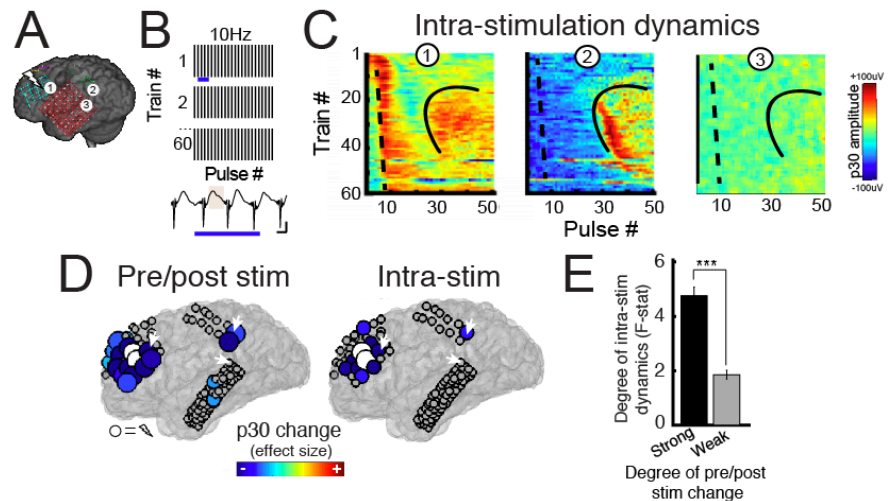


Figure 5: Intracranial 10Hz stimulation elicits complex p30 changes that lead to long-term effects. A) Electrical stimulation paired with intracranial EEG recordings. Lightning bolt = stimulation site. B) Schematic of heat maps of p30 responses to each pulse and train. Bottom: Single trial p30 responses from five consecutive pulses. C) Evolution of intra-stimulation p30 changes. Each colormap represents the p30 response to each stimulation pulse at several brain regions (denoted by circles on brain). Note that the early p30 increase becomes delayed as stimulation progresses (dotted line), and a p30 increase later in the train occurs midway into stimulation (arc), while some regions show no change (#3). D) Spatial correlation of pre/post and intra-stimulation p30 effects. 10Hz stimulation suppressed the p30 in blue regions. Arrows denote regions 1-3 in C. E) Regions with strong pre/post p30 suppression exhibited the strongest degree of intra-stimulation p30 suppression.

response of the p30. A GUI to visualize the online temporal and spatial distribution of these changes will provide real-time feedback to identify where and how strongly the brain is changing. Of note, while I focus efforts on the p30, this platform will have maximal flexibility to quantify all TEP components for use with other disorders and stimulation treatments.

Potential pitfalls. Inability to apply artifact rejection algorithm to resolve the FPN p30 in real time.

Computational processing speeds continue to improve, so problems are unlikely, especially as similar approaches have been applied to EEG data for different applications³⁶. However, if brain features <50ms before stimulation onset are necessary to determine the subsequent stimulation pattern, quantification will be restricted to recordings in the fronto-parietal network to reduce computational resources.

C2. Aim 2: To identify the stimulation parameters that causally and maximally suppress the p30.

Rationale and significance: Several rTMS patterns are clinically utilized, but why one pattern is used depends more on time and insurance constraints than mechanistic understanding. To move beyond this approach, we must better understand the ‘plasticity signature’ of how each rTMS pattern differentially affects brain dynamics. While 10Hz is standard, rTMS at low (1Hz) and high (5, 10, 20Hz) frequencies are all utilized in the clinic. Frequencies >20Hz are not used for safety reasons. ≥5Hz rTMS is thought to be ‘excitatory’ and strengthen the targeted network, while <5Hz rTMS is thought to be ‘inhibitory’ and weaken that network⁶⁶. However, the evidence supporting this claim in non-motor regions in humans is limited. Clinicians currently employ a trial-and-error approach to determine the appropriate frequency. Thus, a mechanistic understanding of how rTMS patterns differentially affects brain plasticity will guide needed improvements in efficacy. This enhanced understanding will form the basis of machine learning generative models that output an optimal stimulation pattern for individual closed-loop treatments.

Preliminary Data: Intracranially, I applied electrical stimulation trains to prefrontal regions while varying stimulation power, duration, and frequency. p30 amplitude decreased with lower stimulation power, shorter duration, and higher frequency (Fig 7). This work suggests that stimulation parameters differentially modulate p30 brain dynamics. Consistent with this finding, 1Hz and 10Hz induced differential effects on the p30¹⁴.

Overview of methods: This aim will translate these intracranial results non-invasively using concurrent TMS-EEG. I will focus on p30 changes for reasons described previously^{14,20}, but exploratory analysis will determine if other (1) TEP components, (2) time-frequency features, or (3) connectivity measures are useful as complementary biomarkers. I will quantify neural activity from the fronto-parietal network (FPN) as it implicated in depression⁸ and rTMS is thought to enhance the connectivity of this network⁵⁸. Source localization⁵⁴ will determine the cortical location of brain change. p30 changes will be recorded before, during, and after rTMS. I will construct intra-stimulation p30 maps (similar to Fig 5) and compare to pre/post changes.

Aim 2.1: I will directly evaluate p30 effects following clinically-utilized rTMS protocols (1, 5, 10, 20Hz and sham rTMS; Fig 8A). Each patient will receive two consecutive rTMS sessions (to test dose response) for each stimulation pattern. I will use clinically standard current intensity (120% of motor threshold, MT) and number of pulses (3,000) for each paradigm. Note that while rTMS is applied daily for one month to treat depression, one

Figure 6: Aim 1: Real-time brain monitoring. A) Noisy rTMS data is recorded from the targeted network. B) A spatial filter for artifact rejection is developed from pre-rTMS data and applied during rTMS. C) The p30 from the FPN is quantified and compared to baseline changes. D) A GUI displays the degree of p30 changes in real-time.

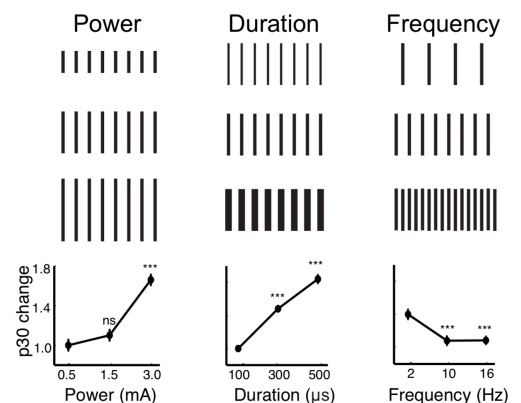
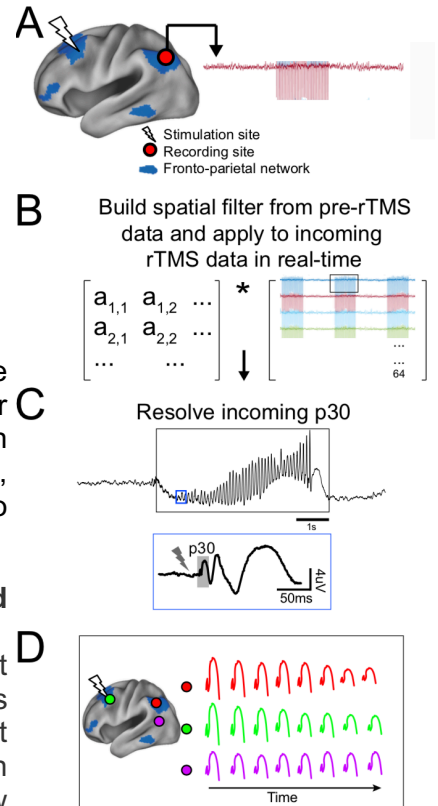


Figure 7: Top: Experimental design to study how stimulation parameters affect p30 changes. Each vertical line represents a stimulation pulse. Bottom: Effects of stimulation parameters on the p30. N=1; ***p<0.01, paired t-test.

or two sessions are often used to study short-term changes and does not affect mood^{67,68}. One week of rest between conditions will avoid buildup of brain changes.

Aim 2.2: From the standard rTMS pattern that maximally suppresses the p30 (Aim 2.1), I will systematically vary stimulation train power, duration, and frequency in an event-related design and evaluate the effect on p30 changes (Fig 8B). For example, if 20Hz rTMS at 40 pulses/train with 120% MT maximally suppressed the p30 for an individual patient, I will vary power (110, 120, 130% MT), frequency (15, 20, 25Hz), and duration (30, 40, 50 pulses/train) around these parameters.

For each stimulation train, I will quantify the pre-stimulation brain activity (*pre-stimulation resting EEG*) and type of stimulation pattern (*stimulation power, duration, and frequency*) and relate this to the brain's response (change in p30). These input/output relationships will be used to create a generative model for optimizing stimulation (Aim 3). I hypothesize that as high frequency stimulation induces long-term plasticity in animal models^{51,69,70}, 20Hz rTMS will induce the strongest p30 suppression. Furthermore, fine-tuning stimulation parameters by increasing train duration and power will further suppress the p30.

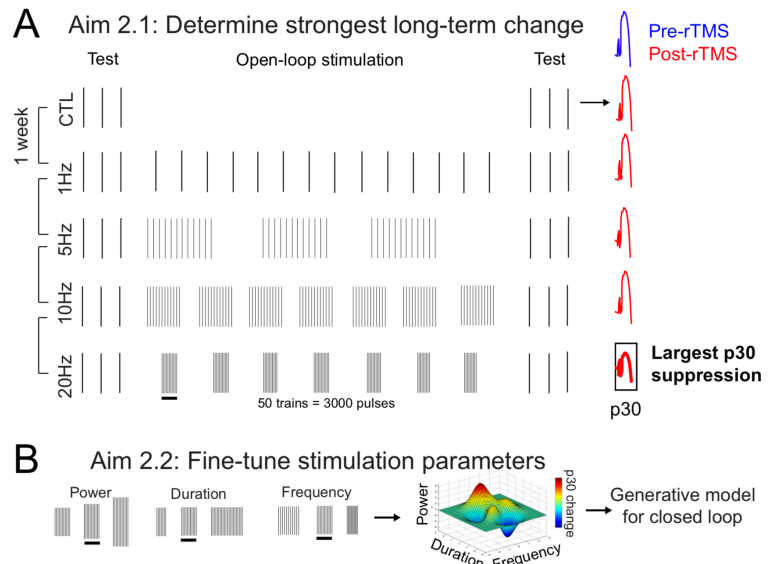


Figure 8: Aim 2: Mapping stimulation to brain changes. Aim 2.1: p30 changes are quantified after each clinically-relevant rTMS condition. The open-loop rTMS pattern that induces the strongest p30 suppression for each patient will be used for Aim 2.2. Aim 2.2: Starting with the strongest p30 suppressor (20Hz in this example), an event-related paradigm will evaluate the effect of power, duration, and frequency on p30 changes. A model is then constructed that maps stimulation patterns to p30 changes.

Potential pitfalls. Minimal p30 change after rTMS. This is unlikely given our preliminary data, but possible that non-invasively we do not observe p30 changes after two sessions. Because other EEG measures such as oscillatory activity are also sensitive to brain changes, I will analyze the time-frequency components of the TMS-EEG response. I will also collect resting EEG before and after rTMS to determine if resting connectivity captures predicted changes. If still no change is observed, I will characterize change across 3-5 rTMS sessions to determine the smallest number of sessions required to induce changes. Finally, a lack of active/sham rTMS separation would suggest that a single session either induces neural changes that are not rTMS specific (e.g., non-specific sensations, auditory click), or from non-neural sources (e.g., from coil pressure or electrode vibration). Experimental controls attempt to minimize these non-neural contributions, but I will revisit these design choices to minimize these effects.

C3. Aim 3: To test whether closed-loop rTMS more strongly suppresses the p30 compared to standard rTMS. Rationale and significance: The convergence of previous aims will be a closed-loop treatment that may more effectively modulate brain networks, improve clinical outcome for treatment non-responders (>50% of patients), and increase the speed and efficacy of treatment for partial responders. This work will also engage computational neuroscientists and engineers to develop more efficient closed-loop interventions.

Overview of methods: Aim 3.1: To devise a maximally-effective closed-loop algorithm, a database relating stimulation patterns and brain states (inputs) to brain changes (outputs) is necessary. This database will be subject-specific and derived from rTMS experiments from Aim 2 (Fig 8). The database will include multiple input parameters (*stimulation power, duration, frequency, and brain state measured with pre-train resting EEG*) and a single output parameter (FPN p30 suppression). Thus, for each subject a database of p30 responses to >300 trains and >10,000 pulses will provide a foundation for the generative model in the closed-loop approach. As the relationship between stimulation patterns and brain changes has not been elucidated, a *multi-layer neural network*⁷¹ will generate this model (Fig 9A). **Aim 3.2:** Using the same set of participants in Aim 2, I will then invert this model using *Bayesian machine learning approaches*⁷² to determine the initial optimal set of stimulation features (e.g. low activity brain state, stronger stimulation, more pulses/train) that maximally suppresses the p30. This model will be updated during stimulation using *control systems theory*⁷³, a branch of engineering dedicated to controlling an action in an optimal manner without delay or overshoot and ensuring control stability.

Three conditions will be randomized, separated by 1 week, and directly compared to each other: 1) open-loop standard rTMS, utilizing the standard rTMS frequency that maximally suppressed the p30 in Aim 2; 2) open-loop optimal rTMS, utilizing the stimulation pattern outputted from the individualized generative model; 3) closed-loop rTMS, starting with the output from the generative model and updating in real-time using control systems. Closed-loop rTMS will be applied based on *multiple input parameters* (Fig 9C; power, duration, frequency, and brain state). The closed-loop algorithm will be programmed to sequentially test how each feature modulates p30 suppression, and feature weights will be adjusted online accordingly. The dose-response of each condition will be directly compared by applying each stimulation pattern for two consecutive days, separated by one week to prevent build-up effects. Boundary conditions will be applied to avoid potentially dangerous or excessively painful levels of stimulation. *I hypothesize that closed-loop rTMS will maximally suppress the p30 compared to open-loop standard and optimal rTMS. Although this aim focuses on the p30, these algorithms will be easily adaptable to other biomarkers as our understanding of rTMS evolves.*

Potential pitfalls. Inability to develop individualized models. Machine learning algorithms often require tens of thousands of data sets to determine an accurate model. Data from Aim 2 should provide sufficient signal to determine individualized models from stimulation/response relationships. However, if not the case, I will instead create a group-averaged model that maps stimulation parameters to p30 changes. I will adjust these weights for each individual based on results from Aim 2 and 3. Closed loop rTMS doesn't outperform open loop. A single rTMS session may not be sufficient, so I will test the dose-response by performing two rTMS sessions for each condition. It is also possible that despite identifying the optimal open-loop stimulation that maximally suppresses the p30 from Aim 2, updating the model in real-time may not yield further benefit. Finally, due to small sample sizes in the previous trial (NCT01829165), another TEP component may more strongly correlate with symptom improvement. Thus, I will continue to analyze incoming data from an ongoing similar but larger open-loop standard rTMS clinical trial (NCT02843373) to identify relevant biomarkers.

C4. Future directions. If closed-loop rTMS is superior in suppressing the FPN p30, I will next perform a clinical trial randomizing a new cohort of patients with major depressive disorder to one month of either daily closed-loop or standard open-loop rTMS, with outcomes focused on FPN p30 suppression and clinical improvement. When other clinical indications are approved (OCD last month and PTSD and substance use trials are near completion), I will apply a similar approach to these disorders. I will develop treatment algorithms individualized to the disorder, the patient's baseline brain circuitry, and response to various stimulation patterns. Finally, real-time monitoring and closed-loop treatment will be adapted to other brain stimulation modalities including vagus nerve and deep brain stimulation.

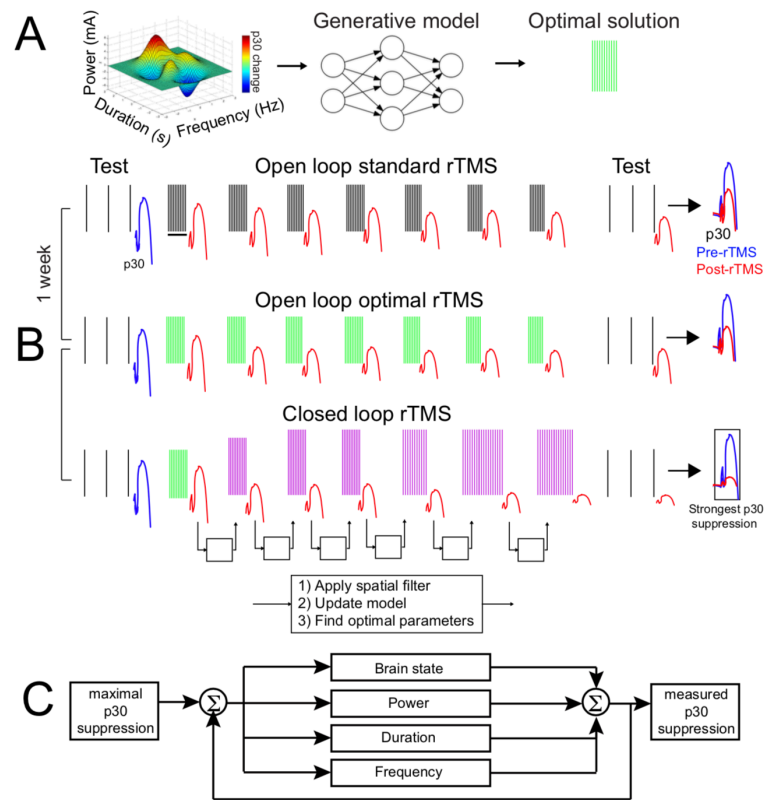


Figure 9: Aim 3: Closed-loop rTMS. A) The database of stimulation patterns and p30 changes will be used to build a generative model. The inverted model will then predict the optimal stimulation pattern (green vertical lines) to suppress the p30. This will be the starting point of closed loop rTMS. B) Three types of rTMS are tested in randomized order over three weeks: *open-loop standard rTMS* using the frequency that maximally suppressed the p30 from Aim 2; *open-loop optimal rTMS* using the output from the generative model; *closed-loop rTMS* starting with the optimal solution from the generative model and updating using control systems. For closed-loop rTMS, after each train, EEG data is cleaned and quantified, feature weights in the model are updated online, and the new stimulation pattern is produced. Purple lines indicate stimulation trains that have been updated using control systems. C) Closed-loop rTMS uses multiple brain features in the control system. The desired effect (maximal p30 suppression) is compared to the actual effect (measured p30 suppression). By minimizing the error term, the model eventually converges on an optimal solution.

C5. Study Structure and Procedures. An intake evaluation will involve the following on subsequent days: 1) eligibility screening, 2) diagnostic interview and questionnaires, and 3) structural MRI for individualized neuronavigation to target rTMS to the left dorsolateral prefrontal cortex. Following intake, subjects will participate in the following set of pilot experiments, each separated by 1 week: 4) open-loop rTMS (Fig 8; 1, 5, 10, 20Hz, sham, event-related) and 5) closed-loop rTMS (Fig 9).

C6. Participants and Feasibility. I will recruit 54 English-speaking, right-handed men and women, ages 18-65, without history of neurological disorders or elevated risk of seizures. Participants require a principal diagnosis of major depressive disorder, made by a Structured Clinical Interview for DSM-5 (SCID-I⁷⁴) and a 24-item HamD⁷⁵ of ≥ 20 to identify patients with high disorder severity. Exclusion criteria are as follows: contraindications for MRIs (e.g. implanted metal), history of head trauma with loss of consciousness, history of seizures or on medications that reduce seizure threshold, neurological or uncontrolled medical disease, history of suicide attempt in past year, active substance abuse, psychotic or bipolar disorders, or a prior history of electroconvulsive therapy or rTMS failure.

While rTMS is FDA-approved for patients who have failed at least 1 medication, results from patients on multiple medications can confound brain findings. Since many patients take a variety of medications, selection of medication-free patients may limit the generalizability of these findings. Nonetheless, I choose to recruit medication-free patients in this study as it focuses on biomarker engagement (and not therapeutic efficacy) and is consistent with my recent p30 finding in medication-free patients. Patients who have been engaged in >3 months of psychotherapy will be recruited for this study. If a patient wishes to initiate antidepressant therapy during this study, I will refer them to a provider and terminate the study.

I aim to recruit 54 medication-free participants over 3 years, with an average of 15-20 per year. Each participant will undergo 15 TMS-EEG sessions, totaling ~200 sessions/year. In the past three years, my advisor Amit Etkin's lab has enrolled 95 medication-free patients per year with similar profiles to that of these patients and completed 550 TMS-EEG sessions on average per year. Thus, these recruitment numbers are feasible.

C7. rTMS. MRI-guided rTMS will be applied to the left dlPFC (10Hz for 5s, 10s rest, 15s duty cycle, 30 minutes and 6000 pulses total) at 120% resting motor threshold (MT), with a MagVenture X100 TMS and a liquid-cooled B65 A/P butterfly coil (MagVenture, Denmark). The TMS coil will be placed above the left dlPFC, chosen from the peak coordinates of a group resting fMRI fronto-parietal network cluster and transformed to individual subject space^{76,77}. Sham rTMS will include 1) a direction-sensor TMS coil that alerts the operators to flip the coil if the wrong side is being used, and 2) low-intensity 10Hz electrical stimulation applied to scalp electrodes under the coil for sham and placed but not activated in the active arm⁷⁸.

C8. Single Pulse TMS. Pulses will be applied every 3 seconds (jittered to prevent entrainment or expectation effects) at 120% of MT for 5 minutes prior to and after rTMS. Participants will be instructed to keep their eyes open and gaze relaxed. Stimulator recharge will be delayed to prevent EEG artifact⁷⁹. A thin (0.5mm) foam pad will be attached to the TMS coil to minimize electrode movement and bone-conducted auditory artifact. White noise matching the frequency of the TMS click⁸⁰ will be provided with noise cancellation headphones to reduce auditory artifact^{79,81}.

C9. EEG Recordings. To record TEPs, I will use a 64-channel high-density EEG (Brain Products, Germany) with pre-amplification and 25KHz sampling rate that reduces noise and stimulation artifact. This system has a large dynamic range to avoid amplifier saturation by the TMS pulse. The amplifier is attached to an active EEG cap (actiCAP, Brain Products) with flat electrodes designed to record without overheating from TMS. Electrode impedances will be less than 5 k Ω to reduce stimulation-related artifact.

C10. TMS-EEG. All data analysis will be carried out in MATLAB (Mathworks, MA) with custom scripts. As the TMS pulse introduces large-amplitude artifacts, multiple stages of artifact rejection are needed before resolving the TEP. Data will be preprocessed using an automated TMS-EEG artifact rejection algorithm⁶ I co-developed. The algorithm involves: 1) interpolation of large stimulation artifact; 2) downsampling (1kHz); 3) independent component analysis (ICA)-based removal of muscle and vibration artifacts; 4) 60Hz line noise removal; 5) high-pass (0.1Hz cutoff) filter to remove slow drift; 6) re-referencing to the common average and epoching (-500 to 1000ms); 7) bad channel and trial rejection; and 8) ICA-based removal of remaining artifacts (e.g., eye blink, EKG). The algorithm showed 96% accuracy compared to manual rejection by EEG experts and outperformed current semi-automated methods.

C11. Statistical Design. Cleaned TEPs will then be baseline corrected, averaged, source localized⁵⁴, and grouped by regions of interest to reduce the number of statistical tests performed. FPN p30 change will be the primary outcome in this study, but other TEP components will also be quantified. TEP changes in Aims 2 and 3 will be analyzed using a longitudinal linear mixed-effects model⁸² to take into account the two consecutive rTMS sessions for each condition. For Aim 2, I will use a 5 group x 2 condition multivariate analysis of variance (MANOVA) to determine the main effects and interactions between rTMS group (1, 5, 10, 20Hz and sham rTMS) and FPN p30 changes (dorsolateral prefrontal and parietal cortex). For Aim 3, I will use a 4 group (closed loop, optimal open-loop, standard open-loop, sham rTMS) x 2 condition (dorsolateral prefrontal and parietal cortex) MANOVA to determine effects specific to each group and region. I will correct for multiple comparisons⁸³ when necessary.

C12. Power Calculations. Power analyses were conducted using GPower⁸⁴ (at 80% power and $\alpha = 0.05$). Power calculation was based on Aim 3, specifically the comparison of *closed-loop vs open-loop rTMS*. Sample sizes were based upon effect size estimates for TEP group differences in the fronto-parietal network. Empirically-obtained effect size p30 suppression estimates following a single session of standard open-loop rTMS (*Keller et al., in preparation*) ranged from 20-40%. I will assume a 20% larger p30 suppression for closed-loop compared to open-loop rTMS. A study with an effect size of 0.3 and a power of 80% will require a total sample of 49 patients to test the association at 5% levels using two-tailed test. Assuming ~10% attrition rate, 54 patients will provide sufficient power for primary aims.

IX. Relationship to previous work. This proposal represents an intersection between new techniques, my clinical training in psychiatry, and my previous work in electrophysiology and brain stimulation. During my PhD, I developed causal brain mapping tools using *invasive* recordings from electrodes implanted in the brain^{15-19,23,25}. During residency, I co-developed fully automated *non-invasive* brain mapping techniques, and applied them in a multi-site clinical trial identifying the brain-based biomarkers for rTMS treatment^{7,11,20,21}. This proposal utilizes several new techniques (control systems, machine learning, real-time monitoring) that capitalizes on my engineering background to develop mechanistically-informed closed-loop brain stimulation therapies. This combination of gaining new skills and building on old will allow me to quickly establish independence while continuing to diversify my scientific interests.

X. Timeline:

	Year 1		Year 2		Year 3		Year 4		Year 5	
Career development and lab management										
Quarterly meetings with advisory committee	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Present at national / international conferences	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Training in responsible conduct of research	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Preparation of NIH R01 grant						✓	✓			
Stanford scientific management course	✓	✓								
Hire research assistant		✓								
Recruit first post-doc			✓							
Recruit first graduate student					✓					
Recruit second post-doc					✓					
Research Strategy										
Specific Aim 1	✓	✓	✓							
Specific Aim 2			✓	✓	✓					
Specific Aim 3						✓	✓	✓	✓	✓

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STANFORD UNIVERSITY Research Consent FormProtocol Director: **Corey Keller, MD, PhD***IRB Use Only*

Approval Date: March 11, 2026

Expiration Date: March 11, 2027

Protocol Title: Investigation of Functional Networks in the Human Brain Using Brain Imaging and Neuromodulation

IRB # 60980

Investigation of Functional Networks in the Human Brain Using Brain Imaging and Neuromodulation

Are you participating in any other research studies? ____ Yes ____ No

KEY INFORMATION SUMMARY

This is a voluntary research study to understand how different types of brain stimulation affects brain activity patterns, with the goal of developing better treatments for mental health disorders. The study involves 1-7 sessions with each session lasting 3-6 hours. You will receive brain imaging (MRI), brain wave recordings (EEG), psychophysiological recordings, cognitive tasks and/or non-invasive brain stimulation (TMS), along with completing questionnaires. The most common risks are mild headache and temporary scalp discomfort, with a very rare risk of seizure from repetitive brain stimulation. While you may not directly benefit since this study uses small doses of stimulation, your participation helps advance our understanding of brain stimulation treatments. If you have depression, you can alternatively receive standard TMS treatment outside this study or discuss other treatment options with your doctor.

INTRODUCTION TO RESEARCH STUDIES

A research study is designed to answer specific questions, sometimes about a drug's or device's safety and effectiveness. Being in a research study is different from being a patient. When you are a patient, you and your doctor have a great deal of freedom in making decisions about your health care. When you are a research participant, the Protocol Director and the research staff will follow the rules of the research study (protocol) as closely as possible, without compromising your health.

The purpose of this research study is to better understand the relationship between the type of brain stimulation used and how it changes brain activity. The goal is to use this understanding to develop a new, personalized brain stimulation for treating mental health disorders. This research study is expected to involve between 1 and 7 sessions depending on the specific research goals. Each session will take approximately 3-6 hours. After a clinical assessment of your symptoms, medical history, medications, and a brain imaging MRI session, you will undergo a series of brain stimulation sessions where we will record the brain changes associated with brain stimulation that measures brain waves. Consent for this study is being sought for research only and participation is voluntary. Common risks include some discomfort with the procedures. Brain stimulation has a very rare risk of seizures. Your mood may change during the study, but as this study only applies small doses of brain stimulation we do not expect this to be common.

PURPOSE OF RESEARCH

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Approval Date: March 11, 2026

Expiration Date: March 11, 2027

Protocol Title: Investigation of Functional Networks in the Human Brain Using Brain Imaging and Neuromodulation

IRB # 60980

You are invited to participate in a research study of brain imaging with magnetic resonance imaging (MRI) and electroencephalography (EEG) aimed at understanding brain changes in response to focal, non-invasive brain stimulation with repetitive transcranial magnetic stimulation (rTMS). EEG measures the electrical current from the brain, displaying brain activation patterns with great temporal resolution. TMS is a procedure that uses magnetic fields to stimulate nerve cells in the brain. Although TMS is an FDA approved procedure for patients with depression who have failed one antidepressant treatment, because you will be receiving small doses of TMS, you may or may not benefit from TMS provided by our study. This study will enroll healthy control participants in addition to participants with major depressive disorder.

After an initial interview that reviews medical and psychiatric history, you may be asked to undergo an MRI scan. In later sessions, you will receive TMS with varying patterns of stimulation. We will record EEG to measure how your brain responds to these different TMS patterns. Each of these procedures are described in detail below.

The knowledge gained from our study will help us learn more about the relationship between TMS patterns and changes in brain networks involved in mood and emotion. This work will help us develop a new type of personalized TMS.

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled. If you decide to terminate your participation in this study, you should notify the protocol director, Corey Keller, MD PhD at 650-498-9111.

This study is being done together by researchers at Stanford University and will include approximately 400 participants.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take up to a maximum of 7 days. Each session will take approximately 3-6 hours.

PROCEDURES

If you choose to participate, Dr. Keller, and his research study staff will ask you to participate in the following procedures:

1. ☐ Psychodiagnostic Interviews, Medical History, and Neurocognitive Assessments:

This baseline screening phase involves an assessment of anxiety or mood symptoms, medical history, and neurocognitive testing. This session lasts no longer than 2-4 hours. The

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assessment will be done by a trained clinical researcher and may involve interviews, completing questionnaires on a computer and doing computer and/or pen and paper evaluations.

We may suggest medication adjustment before enrolling you in our study. Several types of medications used for the treatment of psychiatric disorders could, as a side effect, increase your likelihood of having a seizure. While most medications will not increase the likelihood of a seizure enough to cause concern for including you in this study, our goal is to minimize these risks whenever possible. Therefore the experimenters will discuss with you all prescription drugs or other drugs that you may be taking. If any adjustment of your medication is indicated to include you in this study, we will discuss the options with you and your doctor if you give us permission before you are enrolled in this study. For this study, we also require that you be on a stable medication regimen before enrolling in the study. Please let the researchers know if there are any medication changes in the two weeks leading up to the first study visit. You may be asked to complete a second screening visit after medication adjustments.

It is important for your safety that you discuss any and all drugs that you are taking.

Risks: Answering questions on some of the questionnaires and interviews used in this study may provoke mild feelings of frustration, fatigue, sadness or anxiety. You have the right to refuse to answer any question that makes you feel uncomfortable on any of the questionnaires or interviews. Information you provide will remain anonymous and will be used only for the purposes of the research study. However, it is possible that, based on information gained from this study, the researchers may be required to report information (e.g., information relating to suicide, physical or sexual abuse) to the appropriate authorities.

We will keep your study data as confidential as possible, with the exception of certain information that we must report for legal or ethical reasons, such as suspected child abuse or neglect, suspected elder abuse or neglect, or intent to harm yourself or others.

2. ☐ **Magnetic Resonance Imaging (MRI) scan of the head**

MRI machines use a strong magnet and radiofrequency magnetic fields to make images of the body interior. The scanning procedure is very much like an X-ray or CT scan. You will be asked to lie on a long narrow couch for up to an hour while the machine gathers data. During this time you will not be exposed to x-rays, but rather a strong magnetic field and radiofrequency magnetic fields, which you will not feel. Your head and shoulders lie in a plastic rounded tray, which makes it more comfortable and easier to lie still. You will hear repetitive tapping noises that arise from the Magnetic Resonance scanner. We will provide earplugs that you will be required to wear. The space within the large magnet in which you lie is somewhat confined, although we have taken many steps to relieve the "claustrophobic" feeling. You will have a hand-held control box to manually respond to stimuli.

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As MRI may involve risks to the subject (or the embryo, fetus, or nursing infant if the subject is or may become pregnant), which are currently unforeseeable, if you are pregnant, or currently trying to become pregnant, you may not participate in this study.

Risks: Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electronic devices. If you have a cardiac pacemaker or any other biomedical device in or on your body, it is very important that you tell the operator/investigator immediately. As metallic objects may experience a strong attraction to the magnet, it is also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. All such objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed. In addition, watches, credit cards, hearing aids, and acupuncture should also be removed as these could be damaged. You will be provided a way to secure these items. If you have any history of head or eye injury involving metal fragments, if you have ever worked in a metal shop, or if you could be pregnant, you should notify the operator/investigator. You should also notify the operator/investigator if you have any tattoos on your body, including eyeliner and other permanent makeup. Tattoos could become warm and irritated during the scan and remain so for several days. If you would prefer not to participate in the MR scan due to the presence of tattoos on your body, please inform a research team member.

There is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is expected and should not be painful. Please notify the researchers scanning you if you should experience this sensation.

Dizziness or nausea may occur if you move your head rapidly within the magnet.

The MRI scanner makes loud, periodic sounds that can cause hearing damage. With earplugs or ear protection properly worn, there is no known risk of permanent hearing damage. Rarely, your hearing may be less sensitive for several days after an MRI scan, but if this happens your hearing should return to normal within a few days. MRI sounds could cause ringing in the ears or aggravate any underlying ear conditions like tinnitus (undiagnosed or diagnosed). If you feel any discomfort during the procedure, please notify the operator immediately. You can tell the operator to stop the exam at any time.

IF YOU FEEL DISCOMFORT AT ANY TIME, NOTIFY THE OPERATOR AND YOU CAN DISCONTINUE THE EXAM AT ANY TIME.

Incidental Findings:

The investigators for this project are not trained to perform radiological diagnosis, and the scans performed in this study are not optimized to find abnormalities. The investigators and Stanford are not responsible for failure to find existing abnormalities in your MRI scans. However, on occasion the investigator may notice a finding on a MRI scan that seems abnormal. When this occurs, a radiologist will be consulted as to whether the finding merits further investigation, in

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which case the principal investigator of the research study being conducted will contact you and inform you of the finding. The decision as to whether to proceed with further examination on treatment lies solely with you and your physician. The investigators, the consulting radiologist, and Stanford are not responsible for any examination or treatment that you undertake based upon these findings. Because the images collected in this study do not comprise a proper clinical MRI series, these images will not be made available for diagnostic purposes.

3. ☐ Behavioral testing:

You may be shown images of things, such as simple letters, words, numbers or pictures that will be projected onto a screen in front of you. You may be asked simple questions relating to these letters, words, or pictures. Your responses to these questions will be recorded. This component of the study may happen alone or simultaneously with components 3-5, described below.

Risks: Some pictures or words that you see may provoke mild emotional responses such as fear, disgust, or sadness, though we do not anticipate that this will cause discomfort.

4. ☐ Transcranial Magnetic Stimulation (TMS):

TMS involves a procedure where parts of your brain will be non-invasively (ie indirectly) stimulated by magnetic pulses. These magnetic pulses induce very brief activity in brain areas underlying the TMS coil. You will hear a clicking noise as a few magnetic pulses are produced. To begin, you will sit in a chair and will be asked to wear earplugs to protect your hearing. You may be asked to wear a swim cap for making measurements of your head. A plastic-coated magnetic coil will be held against your head. Stimulation intensity will be calibrated according to the amount of energy needed in the coil to induce activity specifically in your brain. To do so, the researchers will increase the intensity of the stimulation until it causes your thumb to move (when the coil is placed over the part of the brain controlling movement on the other side of the body). Electrodes will be placed on the hand and forearm to record muscle activity. This calibration is done to ensure that sufficient power is used for each individual without excessive stimulation.

TMS may be performed by giving single magnetic pulses to the brain or by giving repetitive pulses (rTMS). During rTMS, you will receive repetitive pulses either continuously when at low frequency (≤ 1 Hz or one time per second) or during brief periods lasting several seconds when at >1 Hz. Stimulation periods will be separated by a rest period, consistent with published TMS safety guidelines. rTMS may also be delivered where the stimulation frequency changes within a session. The parameters may be selected by a computer algorithm, but you will only receive stimulation within the published safety guidelines. At no point will TMS exceed 60 times per second. rTMS does not involve any anesthesia or sedation. You may be asked to take a nap during the TMS session; stimulation may be applied and electroencephalogram (EEG) and/or psychophysiological assessments may be recorded before, during, and after the nap. During some parts of the experiment, you may receive either real or sham TMS. This may also involve weak

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electrical stimulation of the scalp, delivered through two noninvasive electrodes temporarily taped on your skin. For your session, the TMS coil may be held in place manually or with a robotic arm.

Risks: While any procedure has possible risks and discomforts, TMS is considered to be a low-risk procedure. The only common side effect of TMS (approximately 25% of patients) is a mild headache. There are no known significant risks with this procedure at this time because the magnetic fields at the strengths used are thought to be without harm. The exception is if you have a cardiac pacemaker, or a certain type of metallic clip in your body (i.e., an aneurysm clip in your brain). The TMS device could cause discomfort or pain to the head. TMS can be felt as a dull tapping sensation on the head or a hard flick when administered at higher intensities. rTMS can produce a more sharp and uncomfortable sensation. TMS may also cause temporary muscle twitching in hands or the face, in response to the pulses, that can be uncomfortable. It is also possible that you may experience some neck stiffness or neck pain. This is believed to be due to the fact that participants tend to maintain a particular posture of the head and neck during the experiment. If you experience neck stiffness, discomfort, or pain at any point during the experiment, please let us know immediately. Patients who have a history of vasovagal response may experience a fainting episode at the time of TMS. A very small number of patients receiving rTMS have had seizures. All of the reported seizures resolved promptly on their own and none had lasting effects or adverse impact on the patients. There is little evidence of risk of seizures using rTMS the way it will be used in this study. However, there are certain medical factors that could increase the risk of seizure. If any of these apply to you or if you have any questions, please inform the study personnel immediately. In patients with epilepsy, activation of the brain with rTMS could also activate a seizure. Patients with stroke can also develop seizures with rTMS due to the brain scar. Therefore, magnetic stimulation of the brain with rTMS could conceivably activate a seizure in a stroke survivor with such a scar. Those with a history of epilepsy or stroke will be excluded for rTMS studies. However, single-pulse TMS studies have not been found to carry these added seizure risks. For a normal healthy person, producing a seizure from TMS in this experiment is very unlikely. In the unlikely event that a seizure does occur, safety procedures will be followed and you will be closely monitored.

There are no known long-term adverse effects reported with the use of this device. Rarely, device malfunction could result in a scalp burn. There may be unforeseen risks in the long-term that are currently unknown. The TMS device produces a clicking sound. Although studies have found no hearing impairments as a result of this sound, some subjects' experience a mild temporary effect on their hearing. To minimize this possibility, you will be given protective earplugs or noise cancelling headphones. Audio may be played through earbuds or headphones to mask the sound of the TMS device. Although uncommon, some subjects have experienced nausea during the experiment. If this occurs you can discontinue the experiment. Objects such as watches and credit cards should also be removed as these could be damaged. If you are or could be pregnant, the effects of TMS on a fetus are unknown and, therefore, we will not perform the examination at this time. Please take note that some subjects experience a minor headache, migraine or local pain or swelling as a result of the TMS procedure; you may discontinue the experiment at any time. You may also experience temporary and local bruising, swelling, or pain from the swim cap and/or muscle activation by TMS.

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You may be asked to have an electroencephalogram (EEG) or psychophysiological measurement done at the same time as TMS, which does not involve any additional risks when done together with TMS. Please see separate sections on the procedures and risk involved with EEG or psychophysiological assessment.

You may also be asked to undergo/receive repetitive Transcranial Magnetic Stimulation for up to seven days within a two-week period. Multiple sessions may also be held on a single day. There are no known added risks with undergoing rTMS for multiple days. Please see the previous paragraph for details regarding the procedures and risks involved in rTMS.

5. ☐ Electroencephalogram (EEG) and Psychophysiological Assessment

EEG is a test that measures and records the electrical activity of the brain. To collect this information we will ask you to wear a cap on your head that is like a swimming cap. The cap has special sensors attached to it and is connected by wires to a computer. The computer will then record your brain’s electrical activity on the computer screen as wavy lines. We may also put the sensors on your face with a sticky paste to record facial movements and eye-blinking. Electrodes will be attached to your face to measure eye-blink noise, heart-rate, and facial muscles which are associated with frowning and smiling. Finger sensors for skin conductance recordings may be attached to your left index and middle fingers. Electrodes may be placed on hand and forearm to record muscle activity. Electrodes may also be placed on your chin to measure muscle tone or on your face, near your eyes, to measure eye movement. Your gaze may be monitored by an eye-tracking system during some study procedures. You will need to remain awake and alert during the session unless directly instructed to take a nap, in which the applied electrodes will continue to measure data. The test causes no discomfort. The electrodes only record activity and do not produce any sensation.

These recordings may be performed during your TMS sessions (see TMS above). The participant’s breathing rate may also be tracked using 1-2 elastic breathing belts. Electrodes may also be placed on your skin near your wrists, ankles and/or chest area to measure heart activity (ECG). The electrodes only record activity and do not produce sensation.

These recordings may be performed during your behavioral assessments (see Behavioral testing below).

Risks: The rare and minor physical risks associated with EEG are possible skin irritation from the use of electrodes, a mild electrolyte gel, and/or the gel application process. You may feel discomfort due to having electrolyte gel in the hair; however, it is water-soluble and easily rinsed out of the hair. You may also experience fatigue or discomfort from wearing the EEG cap for extended periods of time.

6. ☐ DNA Buccal Sample

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A random sample of participants will be asked if they would like to participate in the DNA buccal/cheek swab. If you choose to participate, the study staff will walk you through the instructions and conduct the salivary samples using a cotton swab in the mouth. They will collect between one to three DNA buccal samples during your study visit(s). You will be asked NOT to eat or drink anything, including water, 30 minutes prior to your saliva collection.

Risks: There are no risks associated with the DNA buccal swap during your study visit(s) and we do not anticipate that this will cause discomfort.

Future Use of Private Information and/or Specimens:

Research using private information and/or specimens is an important way to try to understand human disease. You are being given this information because the investigators want to save private information and/or specimens for future research. Identifiers might be removed from identifiable private information and/or identifiable specimens and, after such removal, the information and/or specimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

Your specimens will be stored in a specimen fridge at Stanford School of Medicine facilities under code number and unlinked. Because your specimens will not be linked to your name after they are stored, you cannot withdraw your consent to the use of the specimens after they are taken.

Genetic Testing and Future Research:

As part of the analysis of your specimens, the investigators will do genetic testing. Genetic research is research that studies genes, including gene characteristics and gene versions that are transmitted by parents to children. Genetic research may include looking at information, such as personal appearance and biochemistry, gene sequences, genetic landmarks, individual and family medical histories, reactions to medications and responses to treatment. Genetic research raises certain questions about informing you of any results. Possible risks of knowing results include: anxiety; other psychological distress; and the possibility of insurance and job discrimination. A possible risk of not knowing includes being unaware of the need for treatment. These risks can change depending on the results of the research and whether there is a treatment or cure for a particular disease.

Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. A Federal law, the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information.

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The process of determining all or nearly all of your DNA sequence is called whole genome sequencing. It is different from genetic testing and does not involve whole genome sequencing because it provides a much more detailed snapshot of your genome. This research might include whole genome sequencing.

The results of the study of your data and/or specimens from this project will be used for research purposes only, and you will not be told the results of the tests.

Y / N I give permission for my samples to be saved for future research, as set-forth above

7. ☐ **Video and Audio Recordings**

Video and audio recording may be requested during your study visits (baseline, active study assessments, follow-ups). The purpose of video and audio recording these sessions is to simultaneously evaluate behavioral data for mood (e.g. smile, frown) and/or physiological data (e.g. pupil size) for our studies. The recordings will be digitally recorded on a HIPAA-secure platform and your name and other identifying information will not be used. All video and audio recordings will be labeled using ID numbers of the participants and will be stored on a secure server only accessible by authorized lab personnel.

We would like you to indicate what uses of these video and audio recordings you are willing to consent to by initialing below. You are free to initial any number of spaces from none to all of the spaces, and your response will in no way affect your credit for participating. We will only use the video and audio recordings in ways that you agree to. In any use of these video and audio recordings, your name will not be identified.

Risks: There are no risks associated with video and audio recording during your study visit(s), and we do not anticipate that this will cause discomfort.

You give consent for your video and audio recordings to be used for the following (please select 'Y' next to the options you give consent to or 'N' if you do not give consent):

Y / N Video and audio recordings can be made during study visits.

Y / N De-identified data extracted from the recordings (e.g. whether your eyes were open or closed at a specific time, whether you were smiling or frowning) can be

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used for our research. This extracted data may be shared in scientific publications, databases, and conferences without sharing your images or audio recordings.

Y / N Identifiable recordings (e.g. pictures of your face) may be shared in scientific publications and conferences. This sharing will not include your name or other protected health information.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the investigators and study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the investigators or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the investigators or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Tell the investigators or research staff if you change your mind about staying in the study.
- If you are a person of child-bearing age, protect yourself against pregnancy by using adequate birth control methods throughout the duration of the study. You agree to tell the study clinician immediately if you think you could be pregnant.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are **free to withdraw** your consent and stop your participation at any time without prejudice to you or effect on your medical care. If you decide to withdraw from the study, you will not lose any benefits to which you would otherwise be entitled.

If you want to stop being in the study you should tell the investigators or study staff. You can do this by phone by calling Dr. Keller at 650-498-9111, or a member of his staff. There are no anticipated consequences to withdrawal from the research study.

The investigators may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions of the investigators and/or study staff.
- The investigator decides that continuation could be harmful to you.
- The study is cancelled.
- Other administrative reason

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- Unanticipated circumstances.
- If you are found ineligible after intake

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions. The specific risks associated with each procedure are described above in the Procedures section.

PEOPLE OF CHILDBEARING POTENTIAL

If you are pregnant or currently trying to become pregnant, you are not eligible to participate in this study. If you are a person who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. You understand that if you are pregnant, or if you become pregnant, you or your child may be exposed to an unknown risk.

You must agree to protect yourself against becoming pregnant during the study. You must accept the risk that pregnancy could still result despite the responsible use of a reliable method of birth control. In this case, you agree to notify the investigator as soon as possible of any possibility of pregnancy, so that appropriate safety measures can be taken. This may result in your being withdrawn from the study.

POTENTIAL BENEFITS

Potential Benefit to you: You may experience a change in your mood, but this is not expected as you will be receiving small doses of TMS. We cannot and do not guarantee or promise that you will receive any benefits from this study.

Potential Benefit to other people: In the future, other people may benefit from the results of this research. New information may lead to improved medical care. However, we will not know whether there are benefits to other people until all of the information obtained from this research has been collected and analyzed.

ALTERNATIVES

For participants with major depressive disorder, you do not have to participate in this research study to receive care for your medical problem. Alternative care may include receiving TMS outside of this study and/or consideration of other medications or therapies, including adjusting the dose of your current psychiatric medication. Please ask your study doctor as many questions as you wish. The doctor's answers to your questions could help you decide whether to participate in this research or receive the standard care that is currently available for your medical problem outside of this study.

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PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director. You will be told of any important new information that is learned during the course of this research study, which might affect you or your willingness to continue participation in this study.

CONFIDENTIALITY

Your identity will be kept as confidential as possible as required by law. Your personal health information related to this study may be disclosed as authorized by you. Your research records may be disclosed outside of Stanford, but in this case, you will be identified only by a unique code number. Identifiers might be removed from identifiable private information and, after such removal, the information could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you. Information about the code will be kept in a secure location and access limited to research study personnel.

Certain scientific journals also require that data used in a published study be contributed in an anonymous, de-identified form to a scientific database. If this is required, all identifying personal information will be removed before it is added to the database. Brain images are stripped of all external identifying characteristics, such as facial features, before submission to an imaging database.

Patient information may be provided to Federal and regulatory agencies as required. The Food and Drug Administration, for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by NIMH which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

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You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

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Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

The purpose of this study is to learn more about connectivity between brain regions and understand how different types of stimulation modify those connectivity patterns. Knowledge gained from this study may further our understanding of how the brain works, and how brain abnormalities lead to psychiatric disorders. Your health information will be kept in secure settings so that only Stanford researchers will have access to any identifying information. This allows us to be certain that your identifying information is linked to the data acquired from you in this study. If this research leads to scientific publications, any and all identifying information will be removed.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your

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information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to: Dr. Corey Keller, 401 Quarry Rd, Stanford, CA 94305.

What Personal Information Will Be Obtained, Used or Disclosed?

Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to the following types of data collected:

Clinical, neurocognitive, behavioral, magnetic resonance imaging (MRI), electroencephalogram (EEG), psychophysiological (including heart rate, respiration, pupil size, eye tracking, skin conductance), transcranial magnetic stimulation, and combinations of the above.

PHI obtained will include name, email address, phone number, mailing address, and social security number. This information will be used for communications and reimbursements during the study.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- Corey Keller, M.D., Ph.D. (protocol director)
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Stanford Center for Cognitive and Neurobiological Imaging.
- Research Staff

Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- National Institute for Health
- National Institute of Mental Health

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Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?

Your authorization for the use and/or disclosure of your health information will end on 12/31/2031 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?

To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

Signature of Adult Participant

Date

Print Name of Adult Participant

Participant ID:

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FINANCIAL CONSIDERATIONSPayment

Research subjects will be offered \$50 per hour of MRI scan time; \$15 per hour for psychodiagnostics interviews, neurocognitive assessments, EEG/psychophysiological assessments; and \$25 per hour for TMS participation in the study.

Some of these payments are made in increments, which builds up as completion nears, and are based on how many visits have been completed.

If you are able to attend all appointments without having to reschedule any of your original scheduled appointments and you arrive on time (less than 5 minutes late) to your session(s), you will be able to receive an additional \$50 dollars upon your completion of your participation. If for some reason, you are found ineligible after consent, you will be reimbursed only for the assessments completed.

Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa. You may need to provide your social security number to receive payment.

Costs

There will be no costs to you for any of the treatment or testing done as part of this research study.

Sponsor

The National Institute of Mental Health, CTS Pilot, and Sleep Society are providing financial support for the study.

COMPENSATION FOR RESEARCH-RELATED INJURY

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

Participant ID:

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CONTACT INFORMATION

- **Questions, Concerns, Complaints:** If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the principal investigator, Dr. Keller at (650) 498-9111 or kellerlab@stanford.edu. You should also contact him at any time if you feel you have been hurt by being a part of this study.
- **Independent Contact:** If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you? ____ Yes ____ No

Signing your name means you agree to be in this study and that you were given a copy of this consent form.

Participant ID:

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Signature of Adult Participant

Date

Print Name of Adult Participant

Signature of Person Obtaining Consent

Date

Print Name of Person Obtaining Consent

Participant ID: