Theta-burst stimulation modulates criticality and cognitive control

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Principal Investigator*: Andrew Westbrook, PhD

Sponsor: Rutgers University

Grant Title: Subjective Cognitive Effort Indexes Sub-Criticality in the Brain

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Version Number: Not applicable; this is the first version of the protocol.

17 March 2024

CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 17 March 2024

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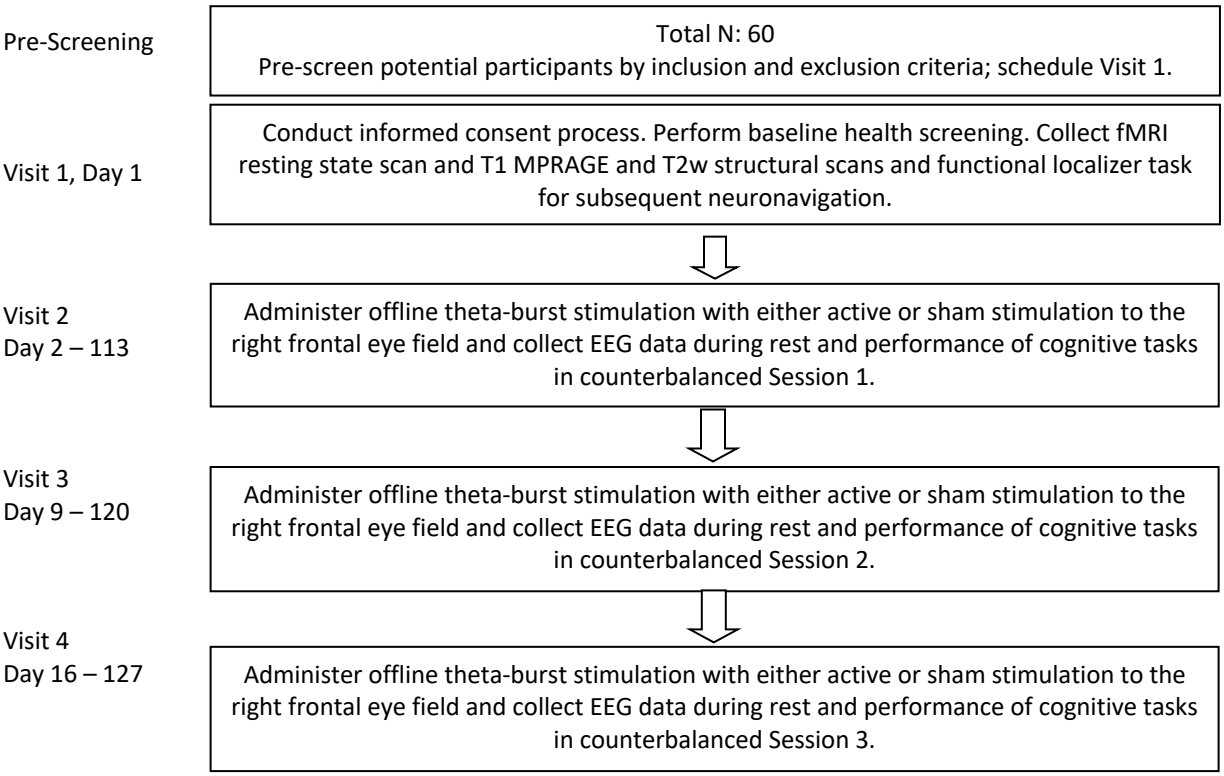
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Theta-burst stimulation modulates criticality and cognitive control
Grant Number:	R00MH125021
Study Description:	In this study we test the hypotheses that critical brain dynamics depend on the balance of cortical excitation to inhibition and that sub-criticality impacts on subjective cognitive effort and cognitive control.
Objectives*:	Primary Objective: Test whether continuous and intermittent theta burst stimulation can alter critical dynamics, cognitive control, and cognitive effort relative to sham stimulation. Secondary Objectives: Test whether the effects of continuous and intermittent theta burst stimulation reflect alterations in the cortical excitation to inhibition balance.
Endpoints*:	Primary Endpoint: Long-range temporal correlations and avalanche branching statistics from EEG signals. Cognitive control performance. Cognitive effort discounting of rewards. Secondary Endpoints: N/A
Study Population:	We will recruit 60 healthy young adults (30 F and 30 M; all 18-45 years old), from the Rutgers University Community in New Brunswick and Piscataway, NJ.
Phase* or Stage:	*N/A*
Description of Sites/Facilities Enrolling Participants:	This single-site study will be conducted at Rutgers University in the Center for Advanced Human Brain Imaging Research. No research will be conducted overseas.
Description of Study Intervention/Experimental Manipulation:	The study will involve three sessions of within-subject, crossover, double-blind, sham-controlled continuous and intermittent theta burst stimulation delivered either at the right frontal eye field.
Study Duration*:	24 months
Participant Duration:	Participants will complete all components within 4 months of their first visit.

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES

	Pre-screening (Pre-consent)	Visit 1 Day 1	Visit 2 Day 63 ±52	Visit 3 Day 70 ±50	Visit 4 Day 77 ±50
Review Eligibility	X				
Informed Consent		X			
Demographics		X			
Clinical history		X			
TMS & MRI compatibility		X			
MRI and Resting State Scans		X			
Outcome Evaluation					
Cognitive control performance			X	X	X

	Pre-screening (Pre-consent)	Visit 1 Day 1	Visit 2 Day 63 ±52	Visit 3 Day 70 ±50	Visit 4 Day 77 ±50
Effort Discounting			X	X	X
Long-range temporal correlations			X	X	X
Avalanche branching statistics			X	X	X
Functional E/I balance			X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

The healthy human brain is a complex, dynamical system which is hypothesized to lie near a phase transition at rest – at the boundary between order and chaos. Proximity to this critical point is functionally adaptive as it affords maximal flexibility, dynamic range, and information handling capacity, with implications for cognitive control. Divergence from this critical point has become correlated with diverse forms of psychopathology and neuropathy suggesting that distance from a critical point is both a potential biomarker of disorder and a target for intervention in disordered brains. We have further hypothesized that subjective cognitive effort is a reflection of divergence from criticality induced by engagement with demanding tasks.

A key control parameter determining distance from criticality in a resting brain is hypothesized to be the balance of cortical excitation to inhibition (the "E/I balance"). Transcranial magnetic stimulation is a widely used experimental and clinical tool for neuromodulation and theta-burst stimulation (TBS) protocols are thought to modulate the E/I balance. Here we test whether we can systematically modulate cortical dynamics away from the critical point with continuous theta-burst stimulation (cTBS) or intermittent theta-burst stimulation (iTBS), which are thought to decrease and increase E/I balance, respectively, and which should, thereby, impact on cognitive control and subjective cognitive effort during performance of the control demanding tasks.

2.2 BACKGROUND

The brain is hypothesized to rest near a critical point and divergence from this critical point is increasingly regarded as an important biomarker for psychopathology and neuropathy (O'Byrne et al., 2022). Importantly, the brain enters a state of sub-critical dynamics when people engage in tasks versus rest (Pfeffer et al. 2018) and becomes even more sub-critical with increasing task demands (Churchill et al., 2016; Kardan et al., 2020). We thus hypothesize that phenomenological, subjective cognitive effort indexes divergence from criticality associated with demanding task engagement. Given that deficient cognitive effort is a core feature of multiple forms of psychopathology (Patzelt et al. 2019, Westbrook and Braver, 2015), it is essential to understand the mechanisms of subjective effort sensitivity. If, as we hypothesize, subjective effort reflects divergence from criticality, we may one day be able to predict subjective effort by measuring a brain's proximity to a critical point, and develop treatments for targeting the mechanisms which underlie divergence from criticality in some individuals.

A key control parameter thought to regulate proximity to criticality is the balance of cortical excitation to inhibition or "E/I balance" (Pfeffer et al. 2018; Agrawal et al. 2018). Prior work has shown that atomoxetine, a norepinephrine reuptake inhibitor, can modulate brain dynamics making them less sub-critical and more closely approximate critical dynamics, even when people are engaged in a task versus rest, consistent with the hypothesis that norepinephrine increases cortical E/I balance (Pfeffer et al. 2018).

Transcranial magnetic stimulation (TMS) is another promising tool for modulating cortical E/I balance and may thereby impact on brain criticality. Specifically, theta-burst stimulation (TBS) protocols have been shown to alternately increase (using intermittent TBS) or decrease (continuous TBS) cortical E/I balance (Desforges et al. 2022; Huang et al. 2005; Chung et al. 2018). TMS is widely used for treatment of depression (Cole et al., 2022), yet the mechanisms of action are unclear. It is therefore tempting to speculate that modulation of E/I balance and critical dynamics contribute to treatment efficacy – especially given that deficient cognitive effort is a core feature of depression (Westbrook et al. 2022). TMS is also an attractive experimental tool by virtue of its capacity to precisely target cortical regions. Since oculomotor control is mediated by the frontal eye fields and performance can be disrupted by TMS stimulation there (Mackey and Curtis, 2017), it is reasonable to posit that modulation of E/I balance and cortical dynamics in the frontal eye fields might mediate oculomotor control and the subjective effort associated with performing such tasks.

Recent studies have demonstrated that it is possible to estimate a functional E/I balance measure from EEG data, based on several minutes of resting EEG data (Bruining et al. 2021). In principle, we should thus be able to estimate the consequences of TBS on cortical excitability more directly, through intrinsic functional dynamics.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Information Risks

The potential for loss of electronic and paper records of personal information used for screening may place the participant at low risk for loss of privacy. The magnitude of this risk is also low as information about an individual participant's behavioral performance on abstract cognitive control tasks and / or their dynamic brain response to task engagement or TMS is of minimal use outside of the context of this experiment.

Physical Risks or Harms

EEG

EEG Devices are categorized as NSR by FDA (https://www.fda.gov/media/75459/download).

MRI

The use of the legally marketed MRI system in research mode will be performed under operating conditions below each of the limits (field strength, Specific Absorption Rate, time rate of change of gradient fields and sound pressure levels) deemed to be significant risk by the FDA as stated in the FDA guidance document, Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices. (https://www.fda.gov/media/71385/download).

There are no known significant risks associated with participation in MRI at the levels of magnetic field proposed here, beyond those due to the effect of a magnetic field on an implanted metal fragment or medical device.

TMS

Overview:

Participating in a TMS study provides indirect benefit to the participants in terms of outstanding scientific knowledge gained about brain function, but it is low risk given that the stimulation parameters being used are within the established safety norms (Rossi et al. 2009; 2020) and we will only enroll healthy participants without contraindication for TMS. In what follows, we detail the specific risks associated with this protocol and the steps we will take to protect against risk beyond those already described in relation to the consent process.

Risks associated with participation in TMS experiments:

(1) Heating, induced voltages, and magnetic field effects. The action of the magnetic field on any implanted or worn metal in, on, or around the head poses a significant risk. Magnetic fields can move or dislodge metal, induce current in conductive metals, cause heating around metal components, and/or affect the operation of any metal device. Thus, it is crucial to screen participants for any irremovable metal in or around the head. Our health screening includes the relevant screening questions.

(2) Hearing changes. Movement of the TMS coil within its casing when current is passed through it produces an audible “click”. Though this click is often not perceived as loud due to the stapedial reflex, it can nevertheless reach 140 dB or more of sound pressure. This exceeds OSHA sound level limits and could produce changes in hearing levels if exposed repeatedly. Thus, we will require all participants to wear earplugs. In addition, we will exclude participants with potential hearing problems.

(3) Induced seizure: Though exceedingly rare even in patients with epilepsy, induction of a “generalized” seizure is the most severe adverse event associated with TMS. A seizure is an episode of excessive brain activity and stiff muscle activity (often referred to as a “convulsion” or “fit”). Seizure risk increases at high stimulator output intensities, at high frequencies of stimulation, with multiple repeated trains of

stimulation, with long durations of stimulation, with short inter-train-intervals, and when stimulating participants with reduced seizure thresholds. However, the risk of seizure induction is minimal to negligible if TMS parameters are kept within the prescribed consensus safety parameters (Rossi et al., 2009; Rossi et al. 2020), and participants are carefully screened for seizure risk. Indeed, over the past decade of experience in both clinical and research domains, this risk has been reduced to the order of one 1 in 89,000 cases (Rossi et al 2020).

(4) TMS application site (scalp) discomfort/headache: The stimulation itself is felt as a tapping sensation on the scalp. The tapping induced by rTMS at high stimulator output intensity can feel sharper and even painful. In addition to a tapping or percussion sensation on the head, muscles and peripheral nerves in the head and face react to TMS with sensations such as twitching of superficial muscle groups. Depending on the location of stimulation, these sensations can be more or less bothersome. The sum of these sensations can range from tolerable to irritating to mildly painful. Beyond informing participants of these risks explicitly during the consent procedures, we will also ask participants about their comfort level throughout the session, and will reduce the stimulator output intensity to their comfort level or stop the session entirely depending on the feedback they give us.

Some individuals who undergo TMS experience a headache, though this may be due to the experimental set up as much as the TMS itself. Headaches usually start after the session (20 mins to 3 hours). In the event of a participant informing us that a headache is coming on during the session, we will allow the participant to cope with the headache in their preferred way, including termination of the session if they wish.

TMS is considered low risk when protocols use stimulation parameters within established international safety norms. Parameters and procedures for all protocols cited here fall within previously published international consensus safety guidelines (Rossi et al., 2009; Rossi et al., 2020) which were incorporated into FDA's Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems in "Table 2. Maximum Safe Train Duration (seconds) Limits for Avoiding Seizures." (https://www.fda.gov/media/81495/download).

(A) Single pulse TMS to primary motor cortex:
Delivery of single TMS pulses (< 1 Hz) over motor cortex will primarily be used in studies of cortical excitability. Single TMS pulses will be delivered at precisely timed points during an experimental trial to either motor cortex. When delivered over motor cortex, the elicited response in EMG of the fingers, hand, or arm will be recorded. These data can characterize changes in the excitability of motor cortex during manipulations of cognitive control due to manipulations of cognitive control or attention. The time between pulses will be irregular, as they are determined by the timings of specific trial events that may not be spaced at regular intervals. However, the minimum time between any two pulses will be 1 second to keep the frequency below 1Hz, and most will be at longer intervals (> 5 seconds).

(B) Offline patterned repetitive TMS:
We may apply rTMS in patterned bursts, using continuous theta-burst stimulation (cTBS) for up to 40 s offline in a single train (of 600 pulses) or, in two trains with the second train after a timed delay (for a total of 1200 pulses). On a separate session we may apply intermittent theta-burst stimulation (iTBS) for … The pattern consists of bursts of three rapid (50 Hz) pulses delivered at a frequency of 5 Hz. In a "spaced" variant of this procedure, two trains are delivered, with a 5-15 minute break in between trains. The spaced variant is advantageous in that it produces more consistent and reliable effects on cortical E/I balance in a meta-analysis (Chung et al. 2018). Importantly, a spaced variant is deemed safe, conforming to the standards articulated in a consensus statement (Rossi et al. 2020). While spaced TBS procedures increase the overall pulse count, they do not increase stimulation intensity or frequency which are of primary concern. At present, spaced TBS procedures with higher pulse counts have been used safely in dozens of studies and hundreds of participants without incident.

Offline TBS has been shown to be effective at eliciting both disruptive and facilitative effects during tasks related to cognitive control and learning. Prior work has shown that TBS effects can last up to 60 minutes following stimulation (Opie et al., 2017; Tse et al., 2018). During this time participants will remain in the lab as the stimulation would be applied in the beginning of the experimental session. This offline technique provides a means of testing the necessity of a brain region for a given task while controlling for the potentially distracting nature of the stimulation itself. It is of higher potency and lasts for a longer duration than other forms of offline stimulation, yet it uses lower intensities and for shorter total durations of stimulation.

(C) Paired pulse TMS
We may apply paired pulse TMS with a pair of single pulses delivered in rapid succession to evaluate the effects of rTMS on long-interval (LICI) and short-interval cortical inhibition (SICI). To evaluate SICI, we will deliver a conditioning stimulus (CS) at 80% of participants' resting motor threshold following rapidly by a test stimulus (TS) of that is strong enough to evoke a motor-evoked potential (MEP) of 1 mV intensity from peak-to-peak. The pair of pulses will be separated by 2 ms when evaluating SICI (Noda et al., 2017a). For LICI, both the CS and TS will be administered with the intensity required to for a 1 mV MEP, and the pulses will be separated by 100 ms (Rogasch et al., 2015). For all experimental sessions, 50-70 pairs of pulses may be delivered with 3-5 s between each pair.

2.3.2 KNOWN POTENTIAL BENEFITS

The proposed research does not guarantee direct benefits to the participants beyond the opportunity to participate in a scientific enterprise. There is a potential indirect benefit of this research as it may advance understanding of the cognitive control of sequences of tasks, knowledge that may have beneficial clinical or societal impact.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

TMS is widely used for both clinical and experimental purposes and has garnered consensus recognition as both safe and effective for altering neuromodulation (Rossi et al. 2009; Rossi et al. 2020). Yet, TMS's effects on cortical function are poorly understood. Thus, studies like this are essential for elucidating the mechanisms by which TMS alters brain function and cognition. Additionally, correlations between critical dynamics and healthy brain functioning, and the use of criticality as a biomarker of psychopathology (O'Byrne et al. 2022), imply the need for studies of those factors which regulate critical dynamics. TMS is a safe and effective method for modulating cortical E/I balance and thus provides a valuable tool for causally testing the role of E/I balance in critical dynamics. The core value of the information to be gained in this study is therefore twofold: 1) it will test mechanistic hypotheses about how theta-burst stimulation protocols alter cortical functioning and 2) it will test hypotheses about the role E/I balance in critical dynamics with implications for oculomotor control as well as subjective cognitive effort.

To enhance the efficacy and precision of the TMS manipulation, we will collect MRI data for each participant prior to their stimulation sessions. The MRI data will provide vital information about brain morphology so that we can direct precision neuronavigation for TMS. This data is vital to ensure that we can target the cortical locations we intend with TMS so that we can make accurate inferences about their respective roles in oculomotor control and subjective effort. MRI-guided neuronavigation is also valuable because it will enable us to make precise inferences about the local effects of stimulation to sites which are commonly used in clinical TMS protocols.

As noted above, the chief risk of TMS studies is seizure, yet this risk is significantly mitigated by well established, consensus guidelines with a proven track record for safe administration (Rossi et al. 2009; Rossi et al. 2020). Key methods for minimizing seizure risk include screening against risk factors among otherwise healthy young adult participants (e.g. epilepsy, history of brain trauma, the use of anti-depressants, etc.). Additionally, we will adhere closely to safety consensus guidelines as articulated by Rossi et al., which have a proven track record of safe administration. Nevertheless, as we cannot rule out seizure risk entirely, every experiment will be run by the PI (Westbrook) or highly-trained staff member and a second experimenter trained to respond quickly and effectively in the event of a seizure. All experimenters will be thoroughly trained, and closely familiar with the protocol for responding including securing the participant to preclude further harm, contacting emergency medical services, remaining with and reassuring the participant until emergency medical services arrive, and subsequently documenting and reporting the incident to our IRB.

For MRI, there are no known risks beyond interactions between metal and the magnetic field. Hence, all participants are extensively screened for implanted metal. Persons at primary or secondary risk based on an implanted object or medical device will be excluded according to MRF operating procedures. Moreover, no personnel are permitted in the scanner room with any metal on their person. As such, we do not anticipate any significant risk from the application of these procedures. In rare cases, a participant

will become anxious because of lying in an enclosed space. We will exclude participants who report a history of anxiety in enclosed spaces, and we will terminate the session of a participant who expresses anxiety about lying in the bore.

All participants will be able to stop the session at any time by squeezing a ball held in one hand. The ball activates a buzzer in the control room. There is also an intercom voice link with the control room that allows verbal communication between participant and experimenters.

To minimize risks around the loss of private information, participant identifiable information will be stored separately from individual data and any screening conversations will take place in private. All electronic records will be maintained on password protected fileservers in a locked office, further protected by firewalls and other security procedures. Paper records will be maintained in locked file cabinets in locked offices.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
Test whether theta-burst stimulation induces a shift towards super- (intermittent theta-burst stimulation, or iTBS) or sub-critical dynamics (continuous theta burst stimulation, or cTBS) in the cortex during rest.	Diminished markers of critical dynamics including reduced long-range temporal correlations measured by detrended fluctuation analysis, and super-critical and sub-critical avalanche branching ratios.	Long-range temporal correlations (< 1.0) and avalanche branching dynamics are widely used metrics of distance from the critical point (degree of sub-: <1.0 and super-criticality >1.0) in EEG studies.	Long-range temporal correlations and avalanche branching ratios of 1.0 are emergent properties of dynamical systems at a critical point. By reducing and increasing the E/I balance, theta burst stimulation should make the brain more sub-critical and super-critical, respectively, thus dampening these

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
			emergent properties.
Test whether theta-burst stimulation to the frontal eye fields (FEF) alters cognitive control relative to sham stimulation.	Increases or decreases in accuracy in the anti-saccade task	Criticality affords the capacity for inter-regional communication in the service of, e.g., top-down control from FEF to saccade motor regions. Thus, people with brains operating closer to criticality should show greater accuracy on the anti-saccade task. If cTBS makes brains more sub-critical, they should show less anti-saccade accuracy. If iTBS makes brains more critical (or even super-critical) during tasks, then it should increase anti-saccade accuracy relative to sham stimulation.	A decrease in the E/I balance in the FEF following cTBS or an increase in E/I balance following iTBS should make brains more sub-critical or more super-critical, respectively, thus decreasing and increasing the capacity for top-down anti-saccade inhibition, respectively.
Test whether theta-burst stimulation to the frontal eye fields (FEF) alters short term memory relative to sham stimulation.	Increases or decreases in accuracy and trial-to-trial variability in the memory-guided saccade task.	Criticality affords greater dynamic susceptibility to afferent inputs. As such, brains operating closer to criticality will more dynamic instability, undermining performance on tasks dependent on short term memory stability. Theta-burst manipulations which push brains closer to criticality will thus produce greater trial-to-trial variability in accuracy and reaction times on tasks	A decrease in the E/I balance in the FEF following cTBS or an increase in E/I balance following iTBS will make the FEF operate closer to criticality for some people and farther away for others. Operating closer to criticality as a consequence of TMS will thereby cause instability in the short-term

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
		including memory-guided saccades.	memory representations needed for memory-guided saccades.
Test whether cTBS increases and iTBS decreases subjective cognitive effort associated with task switching between anti- and pro-saccades.	Task switch costs and effort discounting of rewards contingent on the expenditure of cognitive effort following active versus sham FEF stimulation.	Task switching is effortful and subjectively costly, producing effort avoidance. Brains operating closer to criticality have more dynamical flexibility and so should reduce switch costs and subjective effort.	A decrease in the E/I balance in the FEF following cTBS or an increase in E/I balance following iTBS will make the FEF operate closer to criticality for some people and farther away for others. Operating closer to criticality as a consequence of TMS will thereby cause result more dynamical flexibility reducing the energy required to shift neural dynamics between tasks, and thereby produce lower effort costs.
Secondary			
Tertiary/Exploratory			

4 STUDY DESIGN

4.1 OVERALL DESIGN

The hypothesis to be studied in this Trial is that criticality in the brain depends on the balance of cortical excitation to inhibition and that sub-criticality impacts on cognitive control and subjective cognitive effort. This hypothesis leads to predictions including that TMS protocols which decrease the cortical excitation to inhibition ratio (like continuous theta burst stimulation) will make the brain more sub-critical while protocols which increase the excitation to inhibition ratio (like intermittent theta burst stimulation) will make the brain more super-critical. In turn, when theta-burst stimulation is targeted at regions involved in oculomotor control like the FEF, changes in brain criticality will alter task performance. Specifically, manipulations which make the brain operate closer to criticality will increase susceptibility and information transfer. These functional consequences will thereby lead to worse, more variable performance on tasks which require stability (like memory-guided saccade tasks), lower switch costs and subjective effort associated with task switching (e.g. between anti- and pro-saccade tasks), and better cognitive control (e.g. anti-saccade response inhibition) resulting from better communication between top-down control regions and lower-level sensorimotor effectors.

We will use a double-blind, sham-controlled, crossover, repeated measures design. Specifically, on different days, separated by at least one week, participants will receive continuous theta burst stimulation (cTBS) or intermittent theta burst stimulation (iTBS) with either active stimulation or sham stimulation to their right frontal eye field (FEF). The order of these sessions is pseudo-randomized across participants. Specifically, 20 of our target 60 participants will be randomly pre-assigned to have sham stimulation on their first session (10 sham iTBS + 10 sham cTBS), 20 will have active cTBS on their first session, and 20 will have active iTBS on their first session. The pre-assignment will be determined by permutation of a list of subject numbers using an assignment algorithm that will be executed by a collaborator who is not direclt involved in the study. This collaborator will maintain the blinding codes until de-blinding at the end of the study. Errors in randomization will be documented and session order will be included as a covariate in all analyses.

Participants will come in for four sessions: a first session to complete paperwork and an MRI structural scan and functional localizers scan for subsequent neuronavigation to the FEF, and a resting state scan, and three counterbalanced sessions for sham/iTBS/cTBS stimulation to the FEF. The first stimulation session can happen the day after an MR scan (but no more than 113 days after the MR scan), subsequent stimulation sessions can happen one week after the preceding sessions.

This is a single-site trial.

The interventions are spaced, continuous theta burst (cTBS) or intermittent theta burst stimulation (iTBS) or sham stimulation to either the anatomically-defined or functionally-defined FEF. cTBS will entail two trains of 50 Hz triplet bursts of stimulation delivered at 5 Hz (theta rhythm) continuously for 40 seconds (600 pulses for each train for a total of 1200 pulses) at an intensity based on 80% of a participant's active motor threshold. iTBS will entail brief 2 s trains of 50 Hz triplet bursts of stimulation delivered at 5 Hz (theta rhythm), separated by 10 s for a total of 190 pulses (600 pulses) and, as with cTBS, this total train

will be repeated twice (for a total of 1200 pulses) at an intensity based on 80% of a participant's active motor threshold. These two trains in both cTBS and iTBS will be separated by between 5 and 25 minutes of rest, hence the stimulation is "spaced".

Subjects will be their own controls. The use of subjects as their own controls was selected because it will permit within-participant comparisons of the effect of active versus sham stimulation. While this approach will avoid many random individual difference factors which might confound interpretation of effects relative to a between-participants design, the chief limitation of this design is session order effects. Namely every participant will have target stimulation occurring either first, or after a control stimulation session, and they will also perform the oculomotor tasks either first, or after another session. Session order will be treated as a covariate in all analyses.

The only stratification among participants is gender. There are no expected effects of this stratification.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Participants will serve as their own controls in this repeated-measures design. This design is ideal for avoiding random effects of individual differences unrelated to the constructs of interest and will provide maximal power for detected control versus target stimulation effects. All participants will be healthy, young adults. This group is ideal for studying normal brain function apart from developmental effects and aging effects and without any confounding effects of disease or disorder.

4.3 JUSTIFICATION FOR INTERVENTION

There are few tools for causally manipulating the cortical balance of excitation to inhibition in humans. TMS was chosen as an intervention for modulating E/I balance in the frontal eye field to alter critical dynamics with consequences for oculomotor control and subjective cognitive effort. Transcranial magnetic stimulation has already been shown to modulate cortical E/I balance, and separately to modulate oculomotor control when targeting the FEF. It is widely used, safe and effective. While there are pharmacological means of modulating E/I balance, it is impossible to selectively target the FEF with pharmacological interventions.

A single train of 600 pulses of continuous theta burst stimulation (cTBS) or 600 pulses of intermittent theta burst stimulation (iTBS) is a standard design. We are using a modification involving two trains of 600 pulses separated by 5 to 25 minutes of rest in between, based on a meta-analysis showing that the effects are more reliable and more durable for a spaced cTBS and spaced iTBS design relative to a single train designs (Chung et al. 2016).

We will require three separate stimulation sessions for participants so that we can compare the effects of active versus sham stimulation at the FEF. The sessions will be separated by at least one week providing sufficient time to minimize the chances of carry-over effects from one session to the next.

Three sessions are needed for a within-participants comparison of active versus sham stimulation effects.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the MR scan session, one sham stimulation session and two active stimulation sessions.

The end of the study is defined as completion of the third stimulation session as shown in the Schedule of Activities (SoA), **Section 1.3**.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study and availability for the duration of the study
3. Males and females; Ages 18-45
4. Healthy, neurologically normal with no diagnosed mental or physical illness
5. Willingness to adhere to the MRI and two session stimulation protocol
6. Fluent in English
7. Normal or corrected to normal vision
8. At least twelve years of education (high school equivalent)

Participants will report simply whether they meet screening criteria prior to consent and this data will not be retained. We will only retain data collected after participants give signed written consent and are thus considered enrolled in the study. Participants responding that they do not meet one of the screening criteria will not be enrolled.

5.2 EXCLUSION CRITERIA

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

1. Ongoing drug or alcohol abuse
2. Diagnosed psychiatric or mental illness
3. Currently taking psychoactive medication
4. Prior brain injury
5. Metal in body
6. History of seizures or diagnosis of epilepsy
7. Claustrophobia
8. Pregnant or possibly pregnant
9. Younger than 18 or older than 45
10. Use of medications which potentially lower the seizure threshold

Participants younger than 18 are excluded because there is evidence that cortical excitation to inhibition changes throughout childhood and adolescence and has been associated with an increase in critical dynamics with development (Smit et al. 2011). There is also evidence of increasing excitation to inhibition altering scale-free properties linked to critical dynamics in older adults relative to young adults (Voytek et al. 2015). We are restricting our study to young adults aged 18-45 to avoid any confounds associated with early development or cognitive aging.

Participants will be asked if they are pregnant or possibly pregnant and excluded from participation if they affirm either.

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Come to the study well-rested
- Refrain from using products in their hair to avoid adversely impacting impedance for EEG recordings
- Avoid high amounts of caffeine intake the morning of the study

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include coming back for a stimulation session after receiving a full night's rest, or without products in the participant's hair.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants will be recruited via flyers and announcements which detail core inclusion / exclusion criteria. As such we only anticipate needing to recruit around 65 individuals in order to meet our target (60 participants; 30 male / 30 female) recruitment. Flyers will be posted around the Rutgers University Community, and announcements will be posted in local periodicals and digital message boards, which is appropriate for communicating with a sample of young adults in the target age range. This recruitment strategy has proven successful in recruiting participants who match community demographics in prior study and we anticipate it will remain successful going forward.

Potential participants who see our flyers and announcements will be invited to expressing their interest by emailing us. We will respond to this email with a brief description of what is involved in the study and inclusion / exclusion criteria. Our email will also instruct potential participants to simply say that yes they do or do not meet all of the screening criteria (without specifying which criteria they do / do not meet). If they say they meet all criteria, they are invited to a first session for informed consent procedures. After they give consent, they then fill out detailed screening forms which we retain as part of the study record.

Our anticipated enrollment will approximate the demographics of Piscataway and the Rutgers University community including 26 not Hispanic or Latino and 4 Hispanic or Latino participants. Racial breakdown will approximate 22 Asian, 12 Black or African American, 22 White, and 4 More than One Race participants. All participants will be between the ages of 18 and 45.

To increase the chances that participants come to all study sessions, we will describe the procedures in detail during the recruitment and consenting processes, indicating that we are recruiting participants who would be willing to participate in all sessions (though participants can, at any time, decide to no longer participate and there will be no penalty if that happens). We will also send participants a calendar invite to remind them of their participation and a reminder email the day before their session.

Participants will be paid $20/hour for MRI, or TMS and EEG experiments. Depending on the experiment, participants may have the opportunity to earn additional compensation. Specifically, participants will have the opportunity to select among offers of money to repeat different levels of the oculomotor control tasks for money. Based on their choices, participants may receive an additional ($0.50 to $5.00) in each experimental TMS sessions. This bonus is part of an experimental design intended to assess how people evaluate the subjective costs of cognitive effort.

Participants in MRI are also given an anatomical picture of their brain in digital format if they desire. Participants will be paid in cash, at the end of each experimental session. For participants completing the

three sessions (MRI, active TMS, and control stimulation), their total pay will not exceed $295 across all three sessions ($40 for the MRI session, and $85 each for the TMS sessions).

We do not believe these nominal amounts to be coercive and moreover will inform participants that they can end their participation in the experiment at any time, and they will receive a pro-rated amount of remuneration for their time in the respective session.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

The study intervention is modulation of cortical excitation to inhibition (E/I) balance in the right frontal eye field (FEF) by means of 2 trains of spaced continuous theta burst stimulation (cTBS) or intermittent theta burst stimulation (iTBS) using a transcranial magnetic stimulation device. As prior work (Huang et al 2005; Chung et al. 2018) has shown that cTBS reliably decreases the cortical E/I ratio with diverse cortical targets and iTBS increases the E/I ratio, we expect to replicate a reduction in E/I balance when cTBS is applied to the FEF and an increase in E/I balance when iTBS is applied. The mechanism of action is thought to be a manipulation of inhibitory neurotransmission across diverse timescales. The endpoint of this stimulation will be a modulation of the local E/I ratio that should last at least 60 minutes post-stimulation (Chung et al., 2016).

We will assess the changes in E/I balance by quantifying the functional E/I ratio as previously done in a study of the GABA receptor agonist Zolpidem (Bruining et al. 2020). We furthermore anticipate that a reduction in FEF E/I balance will also make the dynamics of FEF more sub-critical while an increase would make FEF more super-critical (Pfeffer et al. 2018; Poil et al. 2012). Thus, depending on whether participants' brains operate in a sub- or super-critical regime at baseline, we predict that cTBS and iTBS manipulations will either make their brains operate closer to or farther from criticality. If cTBS / iTBS make participants' brains operate closer to criticality, this will be reflected by an inferred functional E/I ratio of 1.0, and stronger long range temporal correlations. Conversely values farther from 1.0 will correspond with weaker long-range temporal correlations otherwise found in the brain in a critical state. Moreover, we will test the prediction that cTBS / iTBS to the FEF will affect oculomotor control. Specifically, we predict that since criticality affords maximal susceptibility and flexibility, tasks which require more stability (e.g. short term memory tasks) will be performed with less precision and more trial-to-trial variability in accuracy and reaction times at criticality. Since criticality also maximizes information transfer capacity,

performance will increase for tasks which require better inter-regional communication (e.g. top-down control tasks) when brains operate near criticality. Hence we specifically predict that TMS manipulations which make the FEF operate closer to criticality will result in worse and more variable memory-guided saccade task performance, and better and more consistent anti-saccade task performance.

Importantly, we will contrast the effects of active cTBS and iTBS with sham stimulation. The double blind procedure involves flipping over the coil so that the participants' experience is as close as possible across active and sham conditions, and the experimenter will have no way of knowing which is which (both sides of the coil are identical and flipped based on an internal blinding code within the stimulator unit) until experimental de-blinding.

6.1.2 ADMINISTRATION AND/OR DOSING

As noted, the intervention is spaced, cTBS and iTBS to the right frontal eye field. Each cTBS session will thus entail two trains of 50 Hz triplet bursts of stimulation delivered at 5 Hz (theta rhythm) continuously for 40 seconds (600 pulses for each train for a total of 1200 pulses) at an intensity based on 80% of a participant's active motor threshold. iTBS will entail brief 2 s trains of 50 Hz triplet bursts of stimulation delivered at 5 Hz (theta rhythm), separated by 10 s for a total of 190 pulses (600 pulses) and, as with cTBS, this total train will be repeated twice (for a total of 1200 pulses) at an intensity based on 80% of a participant's active motor threshold. These two trains will thus constitute the full-dose at the FEF. Sham stimulation will, at random, entail either cTBS or iTBS, with the coil positioned over participants' FEF, but flipped so that it will have no effect on neuronal function.

Each participant will have their own individual set of three stimulation sessions and will thus not interact with other participants during the study.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

All TMS operators will receive training on the two key variables which may affect the consistency of stimulation. The first is the strength of stimulation intensity. Here, stimulation intensity will be based on participants' active motor threshold, which is diagnosed with the use of TMS-evoked potentials measured by electromyography and leads attached to participants' right hand, pursuant to a single pulse to their motor cortex hand knob. Motor thresholding will be based on a semi-automated threshold detection algorithm which is given feedback about the efficacy a given pulse for eliciting a motor evoked potential of 100 microvolts from peak to trough. Thus, threshold identification should be standardized across participants, as should corresponding stimulation intensities.

The second degree of freedom is the precision of TMS targeting. For both motor threshold detection, cTBS, and iTBS, it is important to ensure precise targeting (of the hand knob and FEF for motor thresholding and rTMS, respectively). To ensure consistent targeting, we will use participant-specific structural MRI scans coupled with 3D vision-based neuronavigation systems. The neuronavigation system gives real-time feedback for precision targeting. Also, the exact location of every single pulse is recorded during stimulation, to ensure consistency in targeting.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All participants will complete both one sham and two active stimulation sessions, but the order of these sessions will be pseudo-randomized. Specifically, participants will be assigned participant ID numbers based on their order of recruitment, but the participant ID numbers will be pseudo-randomized with respect to double-blind-coded active versus sham stimulation. Pseudo-randomization of double-blind codes will be generated by a script and saved in a digital file. The de-blinding key to this digital file will be saved by a collaborator not directly involved in conduct of the study and will not be accessed by study personnel until the end of data collection.

The specific session that a participant is in (active versus sham stimulation) will be unknown to the experimenter since the stimulator is only set to function in active or sham stimulation model based on the double-blind codes. To maintain blinding, the experimental condition will not be explained to the participant until after the conclusion of data collection, at the participants' request.

While it may be possible for some participants to infer the distinction between active and sham stimulation, we will not discuss conditions with participants nor will we discuss with participants our predictions about how active versus sham stimulation should differentially impact oculomotor control.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Participation in all four sessions (MRI and three stimulation sessions) is mandatory for participants to remain active participants in the study. Participation will be tracked across sessions by a single ID number associated with all data collected across the three sessions. All study components will be completed within one of the four sessions, so there is no issue of adherence beyond those four sessions.

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Reasons for discontinuation of a stimulation (TMS) session include discomfort or expressed desired to discontinue a TMS session. Some individuals receiving TMS, for example, have reported headaches associated with stimulation and may request discontinuation.

When a subject discontinues from a TMS session, and a clinically significant finding is identified after enrollment, the investigator will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Identification of brain abnormalities during the MRI scan
- Non-compliance with regards to cognitive task instructions
- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study; With TMS an unlikely but possible medical condition would be onset of a seizure
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to appear for the MRI session, or appear or return for two scheduled stimulation sessions and study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to return for a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit within one week, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (3 emails). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

During the screening process, participants will be informed about basic inclusion / exclusion criteria after they first contact us, by email. We will then ask participants questions, by phone, on the MRI and TMS screening forms in detail and indicate whether they meet criteria or not. Although we will not yet ask participants to fill out these forms (i.e. no data will be recorded at this stage), we will ask them to confirm that they meet all criteria on the forms, prior to scheduling their first visit. Within two weeks of this confirmation, we will invite participants for their first session visit.

At the first visit, participants will complete the informed consent process and then be asked to fill out the screening forms, after giving consent. These data will include information about psychiatric or psychological history, presence or absence of metal in the body, history of physical trauma to the brain, current alcohol or drug abuse, current use of psychiatric medications, and use of other medications which may lower the seizure threshold. We will also collect basic demographic and handedness information.

Following the informed consent process the following data will be collected during the study.

- **Performance-based assessments**: Oculmotor task performance, decision-making task performance
- **Questionnaires**: The Need for Cognition Scale
- **Imaging assessments**: Using a 64-channel EEG system, we will record brain waves at the scalp throughout all procedures during the stimulation session. In the MRI scanner we will collect several types of scans. For the purposes of TMS neuro-navigation, we will collect T1 MPRAGE sequences, structural localizer scans, functional localizer scans, and a field map scan. We will also collect 10-12 minutes of resting state fMRI data. These data will be collected on a 3T MRI.

8.2 SAFETY ASSESSMENTS

N/A

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related***.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Any adverse event that (i) results in death; (ii) is life-threatening (places the subject at immediate risk of death from the event as it occurred); (iii) results in inpatient hospitalization or prolongation of existing hospitalization; (iv) results in persistent or significant disability/incapacity; (v) results in congenital anomaly/birth defect; or (vi) based upon appropriate medical judgement, may jeopardize the subject's

health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

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

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study procedures, there is a reasonable possibility that the study procedures caused the AE, or there is a temporal relationship between the study procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.
- **Not Related** – There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise in transcranial magnetic stimulation will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered

unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The Principal Investigator will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Reportable Events
Principal Investigators must report to Rutger's HRPP the occurrence of any of the events described below, collectively referred to as Reportable Events:

- Any Adverse Event (AE) that (1) is a UAE and (2) is related or possibly related to participation in the research.
- Any UP.
- Any breach of Privacy or Confidentiality, including lost or stolen confidential information of a research participant.
- Any medical, procedural, or laboratory error potentially increasing risk to participants (e.g., errors in drug administration or dosing, surgical or other procedures, testing of samples, or test results).
- Any interim analysis, safety monitoring report, publication in a peer-reviewed journal, or other finding indicating that there are new or increased risks to subjects or others, or that subjects are less likely to receive any direct benefits from the research study than as initially presented to the IRB or HRPP.
- Any complaint by or on behalf of a subject indicating that the rights, welfare, or safety of the subject have been adversely affected.
- Any change in the Food and Drug Administration (FDA) labeling; any change in the status of an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE); any withdrawal from market; any manufacturer alert from the sponsor of the research study; or any recall of an FDA-approved drug, device, or biologic under investigation in the research study.
- Any event that requires prompt reporting to the sponsor of the research study, when applicable.
- A Suspension or Termination of a research study or of a study's enrollment, including by the FDA or the sponsor of the research study, based on information indicating that the research study places subjects at an increased risk of harm than was previously known or recognized.
- Any other event that is unanticipated (irrespective of any "relatedness" to the research) and indicates that the research study places subjects or others (e.g., other investigators, research assistants, students, the public, family members or partners of subjects) at an increased risk of harm or otherwise adversely affects the rights, welfare, or safety of subjects or others.

Reporting Timeframes

Principal Investigators must report Reportable Events to the HRPP in accordance with the following timeframes:

- Reportable Events that are either life-threatening or have resulted in death must be reported to the HRPP via telephone, or email if phone is not possible, within one business day from the date the PI is notified of or discovers the Reportable Event. The PI must ensure that Research Personnel are trained to report any Reportable Event to the PI promptly upon discovery, and no later than 24 hours following its discovery or occurrence. A Reportable Events Form must be submitted to

the HRPP within 48 hours of the PI's initial verbal or email notification to the HRPP of the Reportable Event.

- Reportable Events that are not life-threatening and have not resulted in death must be reported to the HRPP in writing as soon as possible, and no later than 7 business days from the date the PI is notified of or discovers the Reportable Event.
- Minor Protocol Deviations must be reported to the HRPP in writing at the time of continuing review when continuing review is applicable to the study protocol, and must be reported during any quality assurance/quality improvement assessment by the HRPP. If continuing review is not applicable to the study protocol, the PI must maintain Minor Protocol Deviations as part of the study record and make the study record available upon request to the IRB, HRPP, and/or any federal sponsor or regulatory agency, as applicable.

Reporting Reportable Events

In accordance with the timeframes outlined above, PIs must submit to the HRPP a Reportable Events Form and include the following information:

- Identifying information for the research study, including the study title, the PI's name, and the IRB protocol number;
- A detailed description of the Reportable Event, including relevant dates and times;
- A detailed description of any corrective action or change to the protocol, planned or already taken, to ensure that the Reportable Event is corrected and will not occur again;
- An assessment of whether any research participants or others were placed at risk as a result of the Reportable Event, or suffered any physical, social, or psychological harm and any plan to address these consequences; and
- Any other information deemed relevant by the PI

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The PI will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the NIH and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 7 working days after the event.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Incidental findings related to the structural MRI scans are possible. MRIs are collected at the Rutgers' Center for Advanced Human Brain Imaging Research and any possible incidental findings will be flagged for review by an MD at Rutgers' Robert Wood Johnson Medical School who will convey any reportable anomalies to participants directly if any are identified.

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

If participants indicate during screening that there is a chance they may be pregnant, we supply and ask participants to take a pregnancy test to ensure that they are not pregnant. If they are pregnant they will be withdrawn from the study and all procedures (MRI, TMS) for safety reasons.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

UPs may warrant corrective actions. Examples of corrective actions or changes that might need to be considered in response to an UP include:

- Modification of inclusion or exclusion criteria to mitigate the newly identified risks
- Implementation of additional safety monitoring procedures
- Suspension of consenting/enrollment of new participants or halting of study procedures for consented/enrolled participants
- Modification of informed consent documents to include a description of newly recognized risks
- Provision of additional information about newly recognized risks to previously consented/enrolled participants.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The principal investigator (PI) will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor/funding agency within 1 business day of the investigator becoming aware of the event
- Any other UP will be reported to the IRB and to the DCC/study sponsor/funding agency within 7 business days of the investigator becoming aware of the problem
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within one month of the IRB's receipt of the report of the problem from the investigator

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

For UPs that impact on all participants, all participants will be notified within two weeks, in writing, of the UP and corrective actions which have been taken.

9 STATISTICAL CONSIDERATIONS

There will not be a formal Statistical Analysis Plan (SAP). Also, no statistical plan will be posted publicly or registered before the study begins.

9.1 STATISTICAL HYPOTHESES

- Primary Endpoint(s):

We predict that, relative to pre-stimulation rest, continuous theta burst stimulation (cTBS) will result in a reduction of the local balance of cortical excitation to inhibition as reflected in the functional E/I balance in proximity to stimulated targets. Conversely, we predict that intermittent theta burst stimulation (cTBS) will result in an increase of the local balance of cortical excitation to inhibition as reflected in the functional E/I balance in proximity to stimulated targets. We also predict these changes to exceed any effects of sham stimulation, and thus another set of endpoints will compare the functional E/I balance after sham versus either active stimulation protocol.

We also predict that, relative to pre-stimulation rest, cTBS and iTBS protocols that will either reduce or strengthen markers of critical dynamics (including, e.g., long-range temporal correlations) in proximity to stimulation targets. The direction of the effect will depend on how the brain operates at baseline. For example a brain that operates in a more sub-critical (lower E/I balance) regime will show an increase in long-range temporal correlations following iTBS (because it should raise the functional E/I balance).

We also predict that, relative to sham stimulation, cTBS and iTBS will alter oculomotor task performance. Specifically, because criticality makes brains more flexible and susceptible, protocols which make brains operate closer to criticality will cause performance to become more variable and worse on the memory-guided saccade task which depends on stability of short-term memory representations. Also, because criticality increases information transfer capacity between brain regions, protocols which make brains operate closer to criticality will cause performance to become better on the anti-saccade task which depends on robust top-down communication of control signals to override bottom-up reflexive saccades to the target.

We also predict that, relative to sham stimulation, cTBS and iTBS will alter subjective effort. We hypothesize that subjective effort reflects divergence from criticality associated with performing difficult tasks. Indeed, typically, brains become more sub-critical, on average, when performing demanding tasks. To measure subjective effort, we will examine cognitive effort discounting – a measure of the amount by which participants discount the offer to perform a more demanding version of tasks (in this case with frequent task switching between anti- and pro-saccades) versus a less demanding version of the task (in this case with minimal task switching between anti- and pro-saccades) for money. The amount of money people forgo to avoid the harder task quantifies the subjective effort cost they experience. We predict

that people whose brains diverge more from criticality during task performance will show steeper effort discounting, and that cTBS or iTBS protocols that minimize divergence from criticality during the task will show shallower effort discounting.

We also hypothesize that subjective effort reflects divergence from a critical state and that criticality depends on the E/I balance. As such, we predict that there will be individual difference correlations in the degree to which TMS perturbs E/I balance, alters measures of criticality including long-range temporal correlations, and ultimately amplifies subjective effort.

9.2 SAMPLE SIZE DETERMINATION

While studies on the effects of continuous theta-burst stimulation (cTBS) and intermittent theta burst stimulation (iTBS) on critical dynamics have never been conducted, power calculations are based on prior work showing that cTBS and iTBS can alter cortical excitability. Effect sizes were taken from a meta-analysis of the effects of cTBS and iTBS on motor cortex excitability, as measured by motor evoked potential via electrodes attached at the contralateral hand (Chung et al. 2016). Two trains of cTBS were found to reliably decrease (Hedge's g 20-30 min after stimulation: g = -1.14), and iTBS reliably increase (g = .84), motor evoked potentials. Using g*Power (Faul et al., 2007), we estimate that if the true effect size remains the same, we will have > 95% power to detect a cTBS effect in a sample of 60 participants at $p < 0.05$. As such, our target recruitment is set at 60 participants (but will recruit additional participants to reach 60 complete participant-session sets, as needed, due to drop-out). At a later timepoint (50-60 minutes after stimulation) two trains of cTBS have a lasting effect of (g = -1.18) while the effects of iTBS are diminished (g = -.21). This means that we should still be able to detect a lasting effect of cTBS with > 95% power at this later timepoint, while power drops to 36% for iTBS.

While effect sizes can vary in rTMS owing to considerable inter-individual differences in response to stimulation, we are taking additional measures to reduce reliability including participant-specific brain images and neuronavigation, and also the use of two, rather than one train of rTMS.

While this estimate is based on motor cortex excitability alone, this outcome is arguably the most direct measure of the effects of rTMS on cortical excitability. Some caution is warranted because it is unclear whether the effects of cortical excitability on motor cortex are predictive of rTMS effects outside of motor cortex.

9.3 POPULATIONS FOR ANALYSES

All participants will be included in all analyses because we are using a within-participant design.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

There are no categorical outcomes. Key measures are all continuous outcomes, and are described in detail in the next section. They will be analyzed according to pre- versus post-stimulation means and also in sham versus active stimulation. We will also report standard errors for each outcome. Key outcomes have multiple associated measures. Multiple measures will be used to assess reliability by parallel forms.

We will use standard frequentist cut-offs of $p < 0.05$ for all statistical tests, correcting for multiple comparisons. Key t-tests will include pre-post and sham-versus-active distinctions in E/I balance measures, oculomotor control task performance measures, and measures of criticality.

Covariates of no interest to be included are sex and age which we will incorporate via multiple regression to ask whether rTMS alters key outcomes (described in the next session).

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The following key outcomes will be assessed in this study. All measures are interval with the exception of the categorical covariate of sex.

- Subjective effort
    - Likert scale ratings (ranging from 1-10) of task-induced effort, demand, time pressure, and stress
    - subjective values as estimated from an indifference point discounting procedure
    - self-reported motivation to engage in demanding tasks on a set of Likert scales with continuous values ranging from 0-20
    - Pupil dilation as a continuous variable which has been shown to index the cognitive and physical effort associated with oculomotor tasks (Koevoet et al., 2024)
- E/I balance
    - fEI derived measure with exponents ranging approximately from 0.0-2.0
    - avalanche branching statistics with values approximately from 0.5 to 1.5
    - power-law exponents with exponents approximating -2.0
- Critical dynamics
    - Long range temporal correlations – a derived measure with exponents ranging approximately from 0.5-1.0
    - Avalanche size and duration distribution exponents approximating -2.0 and -1.5, respectively.

    - Band-limited bistability with values ranging from 0.0 to ~5.0
- Memory guided saccade task performance
    - overall accuracy as degrees of visual angle
    - median reaction times in terms of time from cue until a saccade is launched
    - trial-wise variability in accuracy (SD)
    - trial-wise variability in reaction time (SD)
- Anti-saccade task performance
    - Overall accuracy rate as a percent of trials with correct anti-saccade versus incorrect pro-saccade
    - Median reaction times in terms of time from cue until a saccade is launched
    - trial-wise variability in accuracy (SD)
    - trial-wise variability in reaction time (SD)

Primary analyses of these outcomes will entail multiple regression models in which outcomes will be regressed on cTBS condition (target versus sham), controlling for sex and age.

We will also test for inter-correlations among the primary endpoint measures. Namely, these correlations will test whether the degree to which rTMS alters one measure (e.g. functional E/I balance) correlates with stimulation effects on other measures (e.g. endpoint variability on the memory-guided saccade task).

We will use Pearson's correlations for all tests since our outcome measures are continuous, interval measures.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

N/A

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

N/A

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

N/A

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

We will report individual participant data in terms of their pre- and post- stimulation values for both the active and sham stimulation condition for primary outcomes.

9.4.9 EXPLORATORY ANALYSES

Exploratory analyses we may pursue include testing whether stimulation targeting predicts individual differences in the strength of stimulation effects. We will pursue this question through E-field modeling – a method which estimates the strength of local stimulation based on the actual coil placement and individual participants' brain morphology. We may also ask whether the area in which actual stimulation intensity was the strongest lies within functional connectivity network parcellations and whether that relates to the strength of stimulation effects on behavior.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

In a private room, participants will be given a verbal description of basic study procedures and asked if they have any questions. Next, participants will be given the Informed Consent Document and instructed to read through it carefully, taking as much time as they need, and asking any questions that arise. Finally, if participants and the experimenter are satisfied with the participants' understanding of the procedures, participants will be instructed to sign to indicate their consent to participate.

We are only recruiting fluent English speakers for this study and there is no need to plan for obtaining consent from those who do not speak English. Likewise, as we are only recruiting healthy young adult participants, there is no need to plan for special accommodation to obtain consent for those who are unable to consent on their own behalf.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, the funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, Food and Drug Administration (FDA), or other relevant regulatory or oversight bodies (OHRP).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is

extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator. The study site will permit access to such records.

The study participant's contact information will be securely stored at each site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored on secure, password protected University-run data servers which are only accessible to lab members. This will not include participants' contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by sites and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived digitally.

Although age and sex will be collected, these data are insufficient to identify participants.

Participants' identities will not be conveyed to any third parties.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies
It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored on password-protected research-dedicated servers at Rutgers University. After the study is completed, the de-identified, archived data will be transmitted to and stored at the RUresearch Data Portal hosted by Rutgers University, for use by other researchers including those outside of the study. When the study is completed, access to study data will be provided through the RUresearch Data Portal.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Andrew Westbrook, PhD, PI
Rutgers University
661 Hoes Lane West *Piscataway, NJ 08854*
(919) 360-5399
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As the PI, Dr. Westbrook will oversee the planning and implementation of the study, ensuring that all staff and assistants are properly in safety procedures related to the EEG, MRI, and TMS and that all safety training requirements and protocols are met. Dr. Westbrook will also report any UP or AE to the IRB. Furthermore, Dr. Westbrook will conduct regular reviews of incoming data for Quality Assurance.

10.1.6 SAFETY OVERSIGHT

Safety Monitoring
Participants will be monitored for adverse events by study staff. Significant as well as mild adverse effects of TMS stimulation (seizures, headache) and MRI scanning (claustrophobic reaction, and movement of ferromagnetic objects) will be monitored before and after each TMS and MRI session.

Risk mitigation plan and Trial stopping rules
Three outcomes will be monitored throughout the study as safety endpoints associated with a stop rule.

1. **Number of TMS-induced seizures**: As described above, we will track TMS-induced seizures and clinically significant adverse events requiring outside evaluation. Each stop rule is described in detail below:
    a. More than 1 TMS-induced seizure resulting in hospitalization within any 10 consecutive participants who receive TMS will result in a protocol hold until further evaluation by the PI. Dr. Westbrook has experience with TMS and overseas safety and training compliance for the Core TMS-EEG facility at Rutger's Center for Advanced Human Brain Imaging Research. No new TMS sessions will be administered to any participant once this stop rule is enacted until evaluation of the events is concluded and it is deemed appropriate to proceed. However, participants who have completed their TMS treatments may be scheduled for follow-up visits.

2. **Clinically significant adverse events (i.e. adverse events that require referral for further evaluation) likely related to TMS**. For example, a mild headache after TMS that resolves spontaneously or with over-the-counter medication will not be considered clinically significant. A severe headache that starts during or shortly after TMS and fails to resolve with time and/or OTC intervention would prompt referral to an Emergency Department and will be considered clinically significant.
    a. If more than 1 clinically significant adverse event related to TMS administration and having similar clinical features is seen within any 10 consecutive participants, the protocol will be put on hold until further evaluation by the PI. Follow up EEG visits may continue but TMS will not be administered until the hold is resolved.

3. **Adverse events related to MRI**: Risks associated with MRI scanning will be minimized in the following manner. First, subjects will be screened for contraindications to MRI. In particular, subjects will be excluded from the MRI studies who have a history of moderate or severe claustrophobia, or a history or possible history of any intra-ocular, intracranial, intra-thorax, or intra-abdominal metal or cardiac pacemakers. Subjects will be screened twice prior to the study, once at the time of initial contact, and a second time when they arrive at the MRI facility prior to the study. Anxiety will be minimized by thoroughly explaining the procedures and the nature of the magnetic resonance scanner to subjects prior to study. During the scanning procedures, the subjects are continually monitored visually and auditory for any potential problems, and subjects are assured that they can be removed from the scanner at any time if problems should arise or they are experiencing discomfort. Emergency medical equipment and pharmaceuticals are present at all of the MRI facilities to be used in this project. The development of muscle aches and pains is minimized by providing appropriate cushions at pressure points and beneath the knees as desired by the subject. The appearance of claustrophobia on entering the MRI scanner usually results in termination of the experiment. Earphones and/or earplugs will be used to dampen the sound of the MRI procedure (with a minimum 30 dB dampening effect as per FDA guidelines).

Process of AE/SAE collection, assessing by PI and reporting

The PI will receive access to information on any adverse events that have occurred from study visits and the results of follow-up assessments to assess post-participation changes The PI will report all adverse events according to established IRB guidelines. The study does not involve any invasive procedures. The PI will report findings and recommendations to the IRB. A written report will be provided by the PI to the SO confirming their review of the data and summarizing any recommendations. Furthermore, the PI will be required to report on any significant trends in the data that are indicative of negative or adverse events to the office of the SO.

AE/SAE follow up plan

Participants will be contacted and will again be asked the questions about their reactions to TMS. The PI will confirm that AE's have been appropriately reported and determine whether the risk to benefit ratio has changed.

Data Safety Monitoring

Safety oversight will be under the direction of the PI who has expertise in EEG, TMS, MRI and combined methods like concurrent TMS-EEG. Safety information will be conveyed in the progress report to the Sponsor (NIMH).

1. **Content of report**
    - **a.** Brief description of the trial and progress
    - **b.** Enrollment update and baseline sociodemographic characteristics

c. Retention and disposition of study participants (active, completed, and terminated/withdrawn)
d. Regulatory Issues (amendment, deviations, IRB report, QA issues)
e. AEs and SAEs listings
f. Efficacy (at the end of data collection)

2. **Monitoring activities (initial and ongoing study review)**
   Progress Reports, including patient recruitment, retention/attrition, and SAEs, will be submitted to the PO at the NIMH. Reports will be compiled and will include a list and summary of SAEs. In addition, the Reports will address (1) whether SAE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely.

10.1.7 CLINICAL MONITORING

N/A

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The PI will perform internal quality management of study conduct, and data collection, documentation, and completion.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be initially captured on source documents (see **Section 10.1.9, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

Staff training The PI will be responsible for ensuring that all staff receive proper training with respect to their roles on the study team.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff under the supervision of the PI. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study.

Recorded data including transcribed hardcopy data, digital behavioral data, and EEG data will be saved in a password-protected, research-dedicated server at Rutgers University. Raw MR images will be stored on the Flywheel server at Rutgers University's Center for Advanced Human Brain Imaging Research.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 3 years after the date of Federal Financial Report (FFR) submission. These documents should be retained for a longer period, however, if required by local

regulations. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the PI to use continuous vigilance to identify and document deviations within 5 working days of identification of the protocol deviation. All deviations will be addressed in study source documents. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The PI will be responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be

submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 4 years after the completion of the primary endpoint by contacting the PI. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list). Special terms are those terms used in a specific way in the protocol. For instance, if the protocol has therapist-participants and patient-participants, those terms could be included here for purposes of consistency and specificity.

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event

EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
HRPP	Human Research Protection Program
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.

Version	Date	Description of Change	Brief Rationale
1	10/08/23	Original version	NA
1.1	3/20/24	Change behavioral tasks	New behavioral tasks selected on the basis of greater sensitivity to criticality metrics

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