Causal role of theta and alpha oscillations in output-gating

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CAUSAL ROLE OF THETA AND ALPHA OSCILLATIONS IN OUTPUT-GATING

STUDY CODE: STAR

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ANOVA	Analysis of Variance
BIS/BAS	Behavioral Inhibition System / Behavioral Approach System
CFR	Code of Federal Regulations
Co-I	Co-Investigator
CRF	Case Report Form
DHHS	Department of Health and Human Services
DMV	Department of Motor Vehicles
EEG	Electroencephalogram
EMG	Electromyography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hz	Hertz
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
ITCP	Inter-trial phase coherence
LAR	Legally Authorized Representative
MRI	Magnetic Resonance Imaging
NAMI	National Alliance on Mental Illness
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
OHRE	Office of Human Research Ethics
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SMC	Safety Monitoring Committee
SPI	Serial Peripheral Interface
SOP	Standard Operating Procedure
TMS	Transcranial Magnetic Stimulation
UE	Unexpected Event
UNC	University of North Carolina
UNC-CH	University of North Carolina at Chapel Hill
US	United States
WM	Working memory
WPLI	Weighted Phase Lag Index

STUDY SUMMARY

Title	*Causal role of theta and alpha oscillations in output-gating*
Short Title	*STAR*
Protocol Number	*21-0248*
Phase	*Pilot*
Methodology	*Two phases, five-session, parallel arms design, active control*
Study Duration	*This study is expected to last for three years.*
Study Center(s)	*This is a two-phase, five-session, single-site study performed at the University of North Carolina at Chapel Hill.*
Objectives (Purpose)	*The purpose of this pilot study is to investigate the dynamics between theta and alpha oscillations in the control of working memory.*
Number of Participants	*200*
Diagnosis and Main Inclusion Criteria	*Eligible participants will be healthy adults between the ages of 18-35 with no history of mental or psychiatric disorder.*
Description of Intervention (Procedures/methods)	*The participants will perform a cognitive control task. During the task, rhythmic trains of transcranial magnetic stimulation will be delivered to the prefrontal cortex or parietal cortex. Participants will be screened for their ability to perform the task. Magnetic resonance imaging will be used to source localize regions of interest to be targeted. Electroencephalography will be collected concurrent with stimulation.*
Related IRB Applications	*18-1789*

1 KEY ROLES

1.1 INDIVIDUALS

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1.4 FUNDING SOURCES

Please list below the funding sources for this project:

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NIMH	TBD	R01	TBD	TBD	TBD

External Funding: This project is externally funded through the National Institute of Mental Health (NIMH).

UNC-CH Funding: This project is not funded through UNC-CH.

Classified: This project is not classified.

1.5 SUMMARY OF CHANGES

Summary of changes to protocol:

Version	Date	Reason
2.0	Oct 6th, 2020	Expanded description of the primary and secondary outcomes. Expanded description of the statistical analysis plan. Inclusion of experimental flow figure.
3.0	Jan 29th, 2021	IRB number included to reflect submission.
4.0	March 26th, 2021	Clarification that there are not separate subject IDs for randomization, but that custom scripts handle randomization.
5.0	April 23rd, 2021	Risk of physical injury from MRI and risk of hearing loss from TMS was added to Section 8. Clio Rubinos was included as a medical monitor. Her description was added throughout, for example in Setion 9.2 on Safety Oversight. An incidental findings of MRI protocol was added to Section 8.3.
6.0	May 27th, 2022	Section 5.2 was updated to clarify that MRI is acquired during performance of the working memory task, which is stated elsewhere in the protocol.
7.0	Sept 21, 2025	Randomization was revealed to be parallel arms instead of crossover design. The protocol was updated accordingly to reflect this.

2 INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to U.S. and international standards of Good Clinical Practice (FDA Title 21 Part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

2.1 BACKGROUND

The foundation of cognitive control is the ability of the brain to dynamically allocate limited resources to process input from the environment and manipulate internal representations as a function of behavioral demands (Miller and Cohen 2001, Gazzaley and Nobre 2012). The selective admittance of information from the environment is referred to as "input-gating" (Jensen and Mazaheri 2010). For example, the Posner task guides input-gating by presenting a cue at the start of each trial (pre-cue) that guides attention towards the likely location of a future stimuli (Posner 1980). In contrast, "output-gating" refers to the internal manipulation of previously acquired information, often manifested as prioritization, integration, sequencing, and transformation (Chatham, Frank et al. 2014, Chatham and Badre 2015, Wallis, Stokes et al. 2015). For example, the retrospective-cue working memory working memory task drives output-gating by presenting a cue in the delay period (retro-cue) that indicates in which hemifield items are more likely to be tested (Wallis, Stokes et al. 2015, Souza and Oberauer 2016). Output-gating comprises two intertwined cognitive processes: the *selection of relevant information* and the *suppression of irrelevant information*. These two cognitive processes have been correlated with functional interactions mediated by oscillatory activity in cortical networks in two distinct frequency bands: theta oscillations (4-7 Hz) in selection (Wallis, Stokes et al. 2015, Albouy, Weiss et al. 2017) and alpha oscillations (8-12 Hz) in suppression (Wallis, Stokes et al. 2015, Schneider, Mertes et al. 2016, Poch, Capilla et al. 2017, de Vries, van Driel et al. 2018, Poch, Valdivia et al. 2018).

Theta oscillations are generated in prefrontal cortex during the maintenance of internal representation in working memory (Jensen and Tesche 2002), and the magnitude of theta activity is further increased when internal representations are manipulated, a form of output-gating (Albouy, Weiss et al. 2017, Berger, Griesmayr et al. 2019). Low-frequency neural oscillations in prefrontal cortex are theorized to serve as top-down control signals as they couple to faster frequency activity in posterior cortex (Voytek, Kayser et al. 2015, Helfrich, Huang et al. 2017, Berger, Griesmayr et al. 2019) (see (Helfrich and Knight 2016) for a review). Recent experiments have found that brain stimulation to increase frontal theta activity or theta-frequency connectivity between prefrontal cortex and posterior cortex can improve cognitive performance (Polanía, Nitsche et al. 2012, Alekseichuk, Turi et al. 2016, Berger, Griesmayr et al. 2019, Reinhart and Nguyen 2019). Impaired cognition, especially in executive functions such as working memory, is prevalent in many psychiatric illnesses, including depression (Rose and Ebmeier 2006) and psychotic disorders (Gold, Barch et al. 2018). For example, people with major depressive disorder show decreased theta oscillations during task performance (Kane, Cavanagh et al. 2019). Thus, examining the causal role of theta oscillations in cognitive control will advance not only cognitive neuroscience but also provide a foundation for future investigations into how pathological changes of these oscillations may mediate impairment of cognition.

A complementary process to the selection of relevant information is the suppression of information that is irrelevant for the pursuit of an internal goal. While theta oscillations appear to play a critical role in information selection, alpha oscillations appear to mediate suppression (Jensen and Mazaheri 2010). When irrelevant information is suppressed from further processing, alpha oscillations emerge in the region that would process the information, e.g. alpha oscillations in visual cortex in the presence of visual distractors (Fries, Reynolds et al. 2001). When distractor stimuli are presented in a visual hemifield, the contralateral parietal-occipital cortex exhibits alpha oscillations that correlate with performance (Sauseng, Klimesch et al. 2009). When alpha-frequency TMS is delivered to the parietal-occipital cortex contralateral to distractors, alpha oscillation power is increased (Thut, Veniero et al. 2011) and task

performance is improved (Sauseng, Klimesch et al. 2009). Alpha oscillations are recruited both during input-gating (Sauseng, Klimesch et al. 2009) when attentional cues are presented prior to stimulus presentation and also during output-gating, when attention is shifted between internal representations (Wallis, Stokes et al. 2015).

The neural mechanism for how regions in the brain communicate is via synchronized electrical oscillations (Fries 2015). Therefore, alpha and theta oscillations within the context of output-gating are proposed to serve the critical role of providing functional connections between brain areas. Previous studies have found that connectivity between frontal and parietal regions is critical for cognitive control (Vincent, Kahn et al. 2008, Cooper, Wong et al. 2015, Antzoulatos and Miller 2016). Previous experiments have investigated the causal role of functional connectivity by synchronizing multiple brain regions and putting brain regions out-of-synch using non-invasive brain stimulation (Polania, Nitsche et al. 2012, Alagapan, Riddle et al. 2019, Reinhart and Nguyen 2019). However, there has not been an experiment that has investigated frequency-specific functional connectivity using two different functional bands: theta and alpha.

In this protocol, we investigate the causal role of functional interactions between frontal-theta dependent selection processes and posterior-alpha dependent suppression processes in the context of cognitive control by targeting theta and alpha oscillations in frontal and parietal cortex separately in phase one of the experiment. Theta and alpha oscillations are hypothesized to play complementary roles such that theta oscillations are excitatory (related to active processing) whereas alpha oscillations are inhibitory (related to suppression of processing). Thus, we hypothesize that rhythmic brain stimulation can be used to drive activity in opposite directions as demonstrated in the previous experiment upon which this experiment is built upon (Riddle, Scimeca et al. 2020). In the second phase of the experiment, we target functional connectivity between these regions. In particular, theta oscillations are hypothesized to play a critical role in orchestrating the prioritization and suppression of information across the cerebral cortex. Thus, we hypothesize that in-phase theta frequency connectivity will be causally related to working memory success, but alpha frequency connectivity will be inconsequential and anti-phase theta connectivity will be detrimental. Together these findings suggest an overall model by which the amplitude of theta oscillations in prefrontal and the amplitude of alpha oscillations in parietal play a causal role in prioritization and suppression respectively, but functional connectivity between frontal and parietal cortex within the theta frequency band alone is critical to these cognitive processes.

2.2 DOSE RATIONALE

Transcranial magnetic stimulation (TMS) is a safe, non-invasive, widely-used tool that applies focal electric fields to the brain using magnetic coils placed on the scalp (Rossi et al. 2009). On the first stimulation session of the study, participants will receive a motor thresholding procedure in which electrodes are attached to the first dorsal interosseous muscle of the right hand, or another muscle on the hand or arm that is accessible to be targeted by TMS to the motor cortex. The contralateral motor cortex will be targeted by single pulses of TMS with increased stimulator output until a motor evoked potential (MEP) is generated: defined as a near-instantaneous increase muscle activity greater than 200 microvolts. Next, the intensity of single pulse TMS will be lowered until a MEP is generated on five out of ten pulses. This is defined as the participant's motor threshold (Rossi et al. 2009). If the motor threshold cannot be determined via MEP, the experimenter will use visible twitches as a proxy for MEP. Participants will receive TMS at 120% of their motor threshold. Each train consists of 5 pulses of TMS. Trains are delivered at individualized theta frequency, individualized alpha frequency, or one of two arrhythmic control conditions that matches for the duration of individual alpha frequency (IAF) and individual theta frequency (ITF) with randomized inter-pulse intervals. Thus, "arrhythmic-theta" refers to five TMS pulses with a random inter-pulse interval that lasts the same duration of the theta train of pulses, and "arrhythmic-alpha" refers to five TMS pulses

with a random inter-pulse interval that lasts the same duration as the alpha train of pulses. The duration of the trains is matched to control for non-frequency-specific effects of TMS. The minimum inter-pulse interval will be 20 milliseconds. Between every train will be at least 5 seconds. An inter-train-interval of 5 seconds or greater allows for any residual effects of stimulation to return to baseline. This intensity, inter-pulse-interval, and inter-train-interval is well within the safety guidelines set forth for repetitive TMS (Wassermann, 1998; Rossi et al., 2009) and has been used in similar paradigms as the one described here (Thut et al. 2011; Hanslmayr et al. 2014; Albouy et al. 2017).
For phase one, participants receive trains to either frontal or parietal cortex for each stimulation session (session 4 and 5). For each session of phase one, participants receive trains in theta, alpha, arrhythmic-theta, and arrhythmic-alpha. For phase two, participants receive trains to both frontal and parietal cortex in both sessions (session 4 and session 5) using two TMS coils. In session 4 and session 5, participants will receive stimulation in either theta or alpha frequency. For each of sessions 4 and 5 of phase two, participants receive trains in-synchrony (five pulses delivered to both sites at the same time), anti-synchrony (five pulses delivered to each site with a 180-degree phase difference), arrhythmic-in-synchrony (five pulses delivered to both sites at the same time), and arrhythmic-independent (five pulses delivered to both sites randomly without any temporal relation). Theta frequency functional connectivity is hypothesized to play a causal role in the prioritization and suppression of working memory representations. Alpha frequency stimulation is included as a control to test for the frequency specificity of functional connectivity.
EEG will be collected using the Geodesic 400 system (EGI INC., Eugene, OR, USA). Collecting simultaneous EEG and TMS does not pose any additional risk over TMS on its own. EEG does not involve brain stimulation and is used purely for neuroimaging (minimal risk).

2.3 STUDY AIMS/HYPOTHESES

This study will provide a comprehensive investigation of the causal role and functional interactions between theta and alpha oscillations in the selection and suppression of information processing in the human brain. This will allow us to assess whether these oscillations support dependent cognitive processes, and if this dependence is fundamental in coordinating information processing in the brain.

We hypothesize that theta oscillations in frontal cortex play a causal role in the prioritization of working memory representations and alpha oscillations in parietal cortex play a causal role in the suppression of working memory representations. Furthermore, in-phase theta oscillations, but not alpha oscillations, are critical for synchronizing activity between frontal and parietal cortex. To investigate this model, we propose two phases to the experiment and aims that are defined as either a “primary outcome” or “secondary outcome.” Note that for each of these aims has a corresponding statistical analysis described in section 11.

Phase One overarching goal: Investigate the causal role of frontal theta and parietal alpha oscillations in the prioritization and suppression of working memory representations.

Aim 1 (primary outcome): Stimulation that is aligned to the endogenous activity of the brain (frontal theta and parietal alpha) is hypothesized to improve performance whereas the mismatched frequency of stimulation is hypothesized to decrease performance (frontal alpha and parietal theta). Performance is assessed using Pashler’s working memory capacity metric.

Aim 2 (primary outcome): Stimulation is hypothesized to increase the targeted frequency of stimulation relative to arrhythmic stimulation. This aim will provide evidence of target engagement, i.e. that stimulation is effective at modulating the targeted rhythm.

Aim 3 (secondary outcome): Theta and alpha oscillations are hypothesized to play antagonistic roles

whereby theta oscillations are associated with an increase in neural excitability and alpha oscillations are associated with a decrease in neural excitability. Therefore, we will investigate the impact of stimulation on other frequency band. Theta stimulation is hypothesized to decrease the amplitude of alpha oscillations and alpha stimulation is hypothesized to decrease theta oscillations.

Aim 4 (secondary outcome): Theta oscillations in frontal cortex are hypothesized to play a causal role in precision of working memory representations. During the probe, the participant responds with a specific color from a comprehensive color wheel. Plus or minus 15 degrees around the color wheel is considered "correct." For the correct trials, the precision is calculated as the distance in degrees from the response of the participant to the actual color of the memory item. To investigate if theta oscillations play a causal role in precision, the impact of theta stimulation on precision relative to arrhythmic and as a function of visual field will be investigated.

Aim 5 (secondary outcome): Stimulation that is aligned to the endogenous activity of the brain is hypothesized to entrain neural activity. Inter-trial phase coherence (ITPC) quantifies alignment of neural oscillations across trials. Stimulation in frontal-theta and parietal-alpha is proposed to increase ITPC in a frequency specific manner relative to control stimulation.

Phase Two Overarching Goal: Investigate the causal role of in-phase theta-frequency between frontal and parietal cortex in the prioritization and suppression of working memory representations.

Aim 6 (primary outcome): Stimulation that is delivered in-phase to frontal and parietal cortex in the theta frequency is hypothesized to increased working memory capacity relative to anti-phase theta stimulation. Working memory capacity is quantified using Pashler's metric.

Aim 7 (primary outcome): Stimulation that is delivered in-phase to frontal and parietal cortex in theta frequency is hypothesized to increase functional connectivity between the regions in a frequency specific manner. Functional connectivity will be measured using weighted phase lag index. In addition, we hypothesize that in-phase theta frequency stimulation will increase WPLI magnitude for retro-cues to the right visual field greater than the increase for stimulation with a retro-cue to the left visual field. This hypothesis is motivated by the finding that the left hemisphere processes information for the contralateral visual hemifield and that theta oscillations are linked to the active processing of information.

Aim 8 (secondary outcome): Stimulation that is delivered in-phase is hypothesized to decrease the relative phase difference (phase lag) between the frontal and parietal cortex, whereas anti-phase stimulation is hypothesized to increase the phase lag. If stimulation entrained neural activity directly to the stimulation train, then this pattern of phase lag differences would be expected.

3 PARTICIPANT SELECTION AND WITHDRAWAL

A total of 200 participants will be recruited for this study and all data will be collected at UNC-CH. No specific plans have been made to enroll participants from vulnerable populations. We will collect data until 48 participants have completed the final session for each phase, and we have estimated 100 participants per phase based on our criteria to progress to future sessions and the relatively large time commitment.

3.1 INCLUSION CRITERIA

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

- Between the ages of 18 and 65
- Right-handed

- Able to provide informed consent
- Have normal to corrected vision without color blindness
- Willing to comply with all study procedures and be available for the duration of the study
- Speak and understand English
- Participants will be invited back to the second session only if they are able to perform the task. The criteria for demonstrating the cognitive process of interest is that participants must show a benefit to their working memory percent correct during trials with an informative retro-cue relative to trials with an uninformative neutral cue

3.2 EXCLUSION CRITERIA

A potential participant who meets any of the following criteria will be excluded from participation in the study:

- ADHD (currently under treatment)
- Neurological disorders and conditions, including, but not limited to:
    - History of epilepsy
    - Seizures (except childhood febrile seizures)
    - Dementia
    - History of stroke
    - Parkinson's disease
    - Multiple sclerosis
    - Cerebral aneurysm
    - Brain tumors
- Medical or neurological illness or treatment for a medical disorder that could interfere with study participation (e.g., unstable cardiac disease, HIV/AIDS, malignancy, liver or renal impairment)
- Prior brain surgery
- Any brain devices/implants, including cochlear implants and aneurysm clips
- History of current traumatic brain injury
- Failure to pass a colorblindness test
- (For females) Pregnancy or breast feeding
- Anything that, in the opinion of the investigator, would place the participant at increased risk or preclude the participant's full compliance with or completion of the study

Justifications for any exclusions based on race, gender, or ethnicity: There are no exclusion criteria based on race, gender, or ethnicity. However, non-English speaking individuals are excluded because the ability to accurately and completely communicate study information, answer questions about the study, and obtain consent are necessary.

Justification for excluding women or women who become pregnant: Pregnant participants will be excluded despite the fact that theoretical risk to mother or fetus is exceedingly small, since no safety data for pregnancy is known to exist for TMS studies. Female participants will be asked if there is a possibility that they are pregnant at every stimulation session. If the participant says yes or is unsure, then we will verify pregnancy status via a urine pregnancy test. Only upon a verbal confirmation that pregnancy is not possible or a negative finding will we proceed with the experiment.

3.3 STRATEGIES FOR RECRUITMENT AND RETENTION

3.3.1 RECRUITMENT

The target population of this study includes healthy individuals between the ages of 18 to 45 recruited from UNC Chapel Hill and the surrounding area, including approximately 30,000 candidates for participation.

Recruitment will occur via two methods: flyers to be distributed at major locations on the campus (libraries, gyms, classroom buildings, etc.) and a mass email to all individuals with a UNC-affiliated email address.

3.3.2 RETENTION

Our retention strategy includes a payment schedule of one time per session per participant. The payment amount per hour increases with each session to encourage study completion. The participant will receive payment at the end of each session. The research staff will also give each participant a reminder call or email for upcoming sessions. Each research staff member will be available for the participants to contact via email or phone.

4 BASIC STUDY DESIGN

This study is a pilot, five-session study with transcranial magnetic stimulation (TMS), electroencephalography (EEG), and magnetic resonance imaging (MRI) to understand the neural oscillatory basis of output-gating. The first session of the experiment will be screening session, in which participants provide written consent to participate, screened for colorblindness, complete questionnaires, and perform a working memory task with retrospective cues. Participants will be invited back to the second session if they show a benefit to their working memory percent correct by use of the informative retro-cue relative to the uninformative neutral cue. This session will also be used to select the number of items that will be used in the working memory task for subsequent sessions. The criteria for difficulty titration is task performance between 60% and 85% correct for retro-cue trials and a benefit of at least 5% greater than neutral cue trials. Thus, different participants will perform the task with different numbers of items to be encoded into working memory. Titration of task difficulty as described here is critical for experiments that use causal manipulation (e.g. transcranial magnetic stimulation) to modulate performance. If participants are performing at ceiling (close to 100%) or at floor (close to random change), then any experimental manipulation of behavior is less likely to impact performance as the task is too "easy" or too "hard." For the second session of the experiment, participants perform the working memory retro-cue task while EEG is recorded. In addition, participants will complete a simple perception color task in which participants see a color and choose the matching color from the color circle. This task tests for the precision of perception throughout the color circle. The EEG data from the second session will be preprocessed and a Morlet wavelet convolution analysis will be conducted. The resulting spectrogram will be contrasted between the informative retro-cue and uninformative neutral cue to derive the theta frequency with peak amplitude in prefrontal cortex, and contrasted between a leftward and rightward retro-cue to derive the alpha frequency with peak amplitude in parietal cortex. These peak frequencies will be used for stimulation in the fourth and fifth session. In the third session, we will acquire a structural MRI and resting-state scan (10 minutes) for each participant. The resting-state functional MRI data will be analyzed using independent component analysis. This technique will identify regions in the anterior middle frontal gyrus and posterior intraparietal sulcus that are functionally connected within the frontal-parietal, "executive control," network. A previous meta-analysis of functional MRI studies found that the regions with peak retro-cue activity was at Montreal Neurological Institute coordinates (-40, 36, 28) for anterior middle frontal gyrus and (-38, -48, 44) for inferior intraparietal sulcus. Therefore, we will constrain our search lights to the anatomical landmarks and these coordinates. The center of mass in these regions will be used for targeting

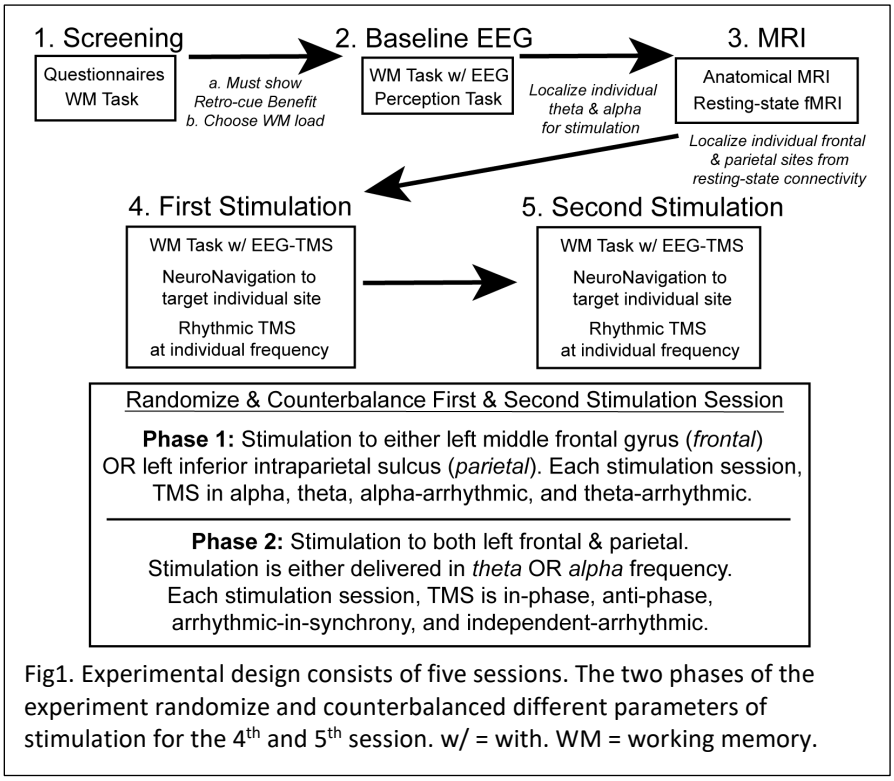

Fig1. Experimental design consists of five sessions. The two phases of the experiment randomize and counterbalanced different parameters of stimulation for the 4th and 5th session. w/ = with. WM = working memory.

with TMS in the subsequent fourth and fifth sessions. In the fourth and fifth sessions, stimulation will be delivered at the timing relative to retro-cue, frequency, and spatial location based on our previous localizers. During stimulation, the location of the TMS coil needs to be aligned to the targeted brain region with neuro-navigation software that records the accuracy of each TMS pulse relative to the target (Localite, Sankt Augustin, Germany). On each trial, the stimulation type will be randomly selected, counter-balanced, and inter-mixed (see section 4.1 below). The effects of rhythmic TMS are not expected to last for more than a few cycles beyond stimulation itself (Thut et al. 2011; Hanslmayr et al. 2014; Albouy et al. 2017). Therefore, the experimental design randomly intermixes the stimulation type within every task block.

4.1 TREATMENT ASSIGNMENT PROCEDURES

Phase one: Participants will receive stimulation to either the frontal or parietal cortex in a randomized and counter-balanced sequence for the fourth and fifth session. Randomization and counterbalancing is performed by a script that generates a spreadsheet to stimulation ID mapping. Participants are randomized upon entering the fourth session of the experiment. Thus, there is no influence of the experiment on which sequence the participant will receive. Stimulation types are randomized and counter-balanced by a script at the time of the session and defined as theta, alpha, arrhythmic-theta, and arrhythmic-alpha. It should be noted that all analyses are controlled by a within-session contrast that accounts for general sequence effects.

Phase two: Participants are randomized to receive stimulation to both the frontal and parietal cortex in either theta or alpha frequency for both of the fourth and fifth session. A similar randomization procedure will be used as in phase one. Stimulation types are randomized and counter-balanced within a session by a script: in-synchrony, anti-synchrony, arrhythmic-synchrony, and arrhythmic-independent. It should be noted that all analyses are controlled by a within-session contrast by comparing to arrhythmic stimulation.

The primary analysis of the experiment is controlled within-session as a contrast with the arrhythmic control conditions. The difference in site of stimulation for phase one and the auditory difference between theta and alpha stimulation (theta is audibly slower than alpha) precludes double-blinding as the researcher will be aware of this difference in running the experiment. In other words, the study cannot be blinded and there is no attempt to blind the study. Furthermore, the control for each stimulation condition is self-contained within each session. The stimulation sessions for each phase consists of four stimulation conditions (described above) and two task conditions (retro-cue to the left visual field and retro-cue to the right visual field), thus there are a total of 8 conditions total for phase 1 and 4 conditions total for phase 2. With 600 trials per session, then will be 75 trials of each condition for phase 1 and 150 trials of each conditions for phase 2. The order of these trials is randomized for each session for each participant via a script.

5 STUDY SCHEDULE

Participants will be recruited for participation by phone call, and phone calls will take place in a private setting.

5.1 SCREENING

The phone screening allows researchers to screen out participants based on self-report responses and for potential participants to become familiar with the study schedule and procedures. During the telephone screening, researchers will provide a brief background about TMS, the timeline of visits, and the time commitment required. The participant will be informed of the compensation amount and payment schedule. The researcher will answer all of the questions posed by the participant. Once all questions have been answered, the participant will be asked if he/she is still interested in participating in the study. If yes, the researcher will ask if the participant will provide verbal consent to begin the initial phone screening which will determine eligibility for the stimulation session. *A*

telephone script, which includes the screening questions, is provided in Appendix G. If the participant is determined to be eligible for participation (no contraindications for TMS or MRI and passes phone screening), then the sessions will be scheduled and a reminder call or email will be given at least 24 hours before each session.

5.2 STIMULATION SESSIONS

Participants will undergo five sessions: one screening, one baseline, one MRI, and two active stimulation sessions. At the first session, participants will be guided through the consent form. To ensure that all aspects of the research are understood, participants may be asked a series of questions about the research they are about to take part in (*Appendix E*). Once it is clear that the participant understands the consent form, then they may sign the form.

Session 1: Screening (2 hours)

- In this initial session, the researcher will explain the procedures for the study, expectations for participation, and participant rights.
- After obtaining written consent, a pregnancy screening will be administered.
- Participant is provided a weblink to completes a series of questionnaires for exploratory purposes. These measures are listed below under "self-report measures." If these questionnaires are not completed prior to the session, then they are completed here.
- The participant will practice and perform the perception task and the retro-cue working memory task. Participants are given a self-paced break between blocks of the task.
- Participant will receive $20 in compensation.

Session 2: Baseline (3 hours)

- EEG net is applied.
- Resting state EEG – Participant will be asked to relax with eyes open and eyes-closed while EEG is collected simultaneously.
- The participant will practice and perform the retro-cue working memory task.
- The participant will practice and perform a simple WM task for color wheel precision.
- Electrodes and net will be removed and participant can wash their hair and face
- Participant will receive $30 in compensation.

Session 3: MRI (1 hour)

- Participant undergoes a structural MRI scan.
- Participant performs up to ten-minutes resting state MRI scan in which participant fixates on a point.
- Participant performs working memory task during functional MRI scans
- Participant will receive $20 in compensation

Session 4 and 5: Stimulation 1 and 2 (3 hours)

- Motor thresholding using single pule TMS for use in future sessions will be performed once for each participant on the first day of stimulation, and held constant for the following stimulation session.
- Before practice and performance of the cognitive control task, the TMS coils will be position over the targeted region.
- During performance of the task, stimulation will be delivered on every trial.

- During stimulation, white noise will be played for the participants to reduce neural effects of auditory entrainment of rhythmic TMS.
- At the end of the session, participants will receive $40, and $60 in compensation for sessions 4, and 5, respectively.

6 STUDY PROCEDURES/EVALUATIONS

6.1 SELF-REPORT MEASURES

Researcher will use a standard questionnaire to screen TMS & MRI candidates. The following questions include the standard contraindications for TMS & MRI research. The TMS contraindications assessment will be administered during the verbal phone screening and for every session prior to stimulation (sessions 4 and 5).

1. Do you have epilepsy or have you ever had a convulsion or a seizure?
2. Have you ever had a fainting spell or syncope? If yes, please describe in which occasion(s)
3. Have you ever had severe (i.e., followed by loss of consciousness) head trauma?
4. Do you have any hearing problems or ringing in your ears?
5. Are you pregnant or is there any chance that you might be?
6. Do you have metal in the brain/skull (except titanium)? (e.g. splint, fragments, clips, etc.)
7. Do you have cochlear implants?
8. Do you have an implanted neurostimulator? (e.g., DBS, epidural/subdural, VNS)
9. Do you have a cardiac pacemaker or intracardiac lines or metal in your body?
10. Do you have a medication infusion device?
11. Are you taking any medications? (Please list)
12. Did you ever have a surgical procedure to your spinal cord?
13. Do you have spinal or ventricular derivations?
14. Did you ever undergo TMS or MRI in the past?

Affirmative answers to one or more of questions 1–13 do not represent absolute contraindications to TMS and fMRI, but the risk/benefit ratio should be carefully balanced by researcher.

In addition to our screening form, we will administer the MRI screening form provided by the Biomedical Research Imaging Center (BRIC) at the University of North Carolina at Chapel Hill. After completion of this form, it is sent to lab technicians at the BRIC who provide additional screening of participants (this form is included in the Appendix). The MRI safety form is completed verbally during phone screening and in person during session 3 (MRI).

In addition, several self-report measures will be collected throughout this study. These measures are listed below and can be found in the attached documents.

A. THE STATE-TRAIT ANXIETY INVENTORY (STAI) is a 20-item self-report assessment that assesses either temporary or chronic anxiety. For the purposes of this study, the state version will be used to measure anxiety as a result of the stress condition. The STAI is commonly used to assess both types of anxiety, and has applications in both clinical and research settings (Spielberger et al. 1983).
B. THE BEHAVIORAL INHIBITION AND BEHAVIORAL APPROACH SYSTEM SCALES (BIS/BAS) are a set of 24 questions used to assess an individual's sensitivity to approach vs. inhibition in motivating behavior. This scale is commonly used to measure behavior and has been demonstrated to be reliable (Carver and White 1994).

C. THE POSITIVE AND NEGATIVE AFFECT SCHEDULE (PANAS) is a 20-item self-report assessment using a 5-level Likert scale to assess the positive and negative affect of an individual over the past week. This scale has been shown to be a reliable measure of both positive and negative affect with little subjectivity to demographic variables (Watson et al. 1988).
D. THE EDINBURGH HANDEDNESS INVENTORY is a 20-item scale to assess the hand dominance of a person in everyday activities (Oldfield 1971).

6.2 SPECIAL ASSAYS OR PROCEDURES

Each participant will receive stimulation in the fourth and fifth sessions, separated by about one week. Motor thresholding will take place in the first stimulation session. For stimulation day, the rhythmic TMS trains are delivered on every trial of the task (there are 600 trials per session). Each train of TMS consists of 5 pulses. There will be a total of 3000 pulses delivered per session in phase one, and with two coils there will be total of 6000 pulses per session in phase two. Each TMS train will be separated by a minimum of 5 seconds. There are three possible trains: individual alpha frequency with an approximate 100 milliseconds inter-pulse interval, individual theta frequency with a 200 milliseconds inter-pulse interval, and arrhythmic with a variable inter-pulse interval (with a minimum of 20 milliseconds inter-pulse interval). The inter-pulse interval, inter-train interval, number of trains, and TMS intensity are all under the safety guidelines set forth by Rossi et al. 2009 and is typical for experiments that deliver online TMS (Hanslmayr et al. 2014; Albouy et al. 2017).

6.3 SAFETY MEASURES

We will be monitoring the safety of our participants throughout the study with the following measures. These measures are listed below and can be found in the attached documents.

A. A stimulation adverse effects questionnaire will be used based on common side effects experience with TMS. This questionnaire will be administered at the end of each session in which the participant receives TMS (sessions 4 and 5). This questionnaire will be used as a safety measure and to collect data on participant experience. Please see *9.1 Safety Parameters* for more information.

6.4 LABORATORY EVALUATIONS

6.4.1 SCREENING LABORATORY EVALUATIONS

A urine pregnancy test will be performed for all female participants.

INSTRUCTIONS FOR SPECIMEN PREPARATION, HANDLING, AND STORAGE. For this evaluation, an FDA approved commercial home-based kit will be used (HCG Urine Pregnancy Test Strip). Results are available after only a few minutes. Once the results are clear, the researcher will make a note and the sample will be disposed. All samples will be handled using single-use disposable medical gloves.

6.5 COGNITIVE TASKS

6.5.1 PERCEPTION TASK

The perception task consists of a single epoch. A colored square is presented at fixation with an empty outline of a square adjacent to it. A color-wheel is presented around these two squares. The participant is given two seconds to choose the color from the color-wheel such that it matches the colored square in the center of the screen. Participants move a joystick towards the direction of the color in the color wheel that they wish to select. The square in the center changes color to match the selected color by the

participant. Once the color is selected, the participant pulls the trigger on the joystick with their index finger. Participants are instructed to be both fast and accurate.

6.5.2 RETRO-CUE WORKING MEMORY TASK

The retro-cue working memory task consists of five epochs. In the first epoch, the participant is presented with lateralized stimuli, colored squares, in both the left and right visual hemifield. The participant is given one second to encode these items into memory. During the screening participants will be presented with one, two, or three colored squares in both visual fields, and in subsequent session there is a fixed number of stimuli. In the second epoch, there is a one second delay period over which the iconic memory of the colored squares decays. In the third epoch, the participant is presented with an informative retro-cue, an arrow to the left or right, that is 100% predictive of the upcoming probe, or an uninformative neural cue, an arrow pointing in both directions. In the fourth epoch, participants must maintain the items in memory over a two second delay. It is during this epoch, after the presentation of the retro-cue that TMS is delivered in sessions four and five. Finally, in the probe epoch participants are presented with a dotted outline of the squares on the left or the right and solid lines around the item to be recalled. At the center of the screen is a color wheel and a blank square. Participants move a joystick towards the direction of the color in the color wheel that they wish to select. The square in the center changes color to match the selected color by the participant. Once the color is selected, the participant pulls the trigger on the joystick with their index finger. Participants are instructed to be both fast and accurate.

7 STUDY INVESTIGATIONAL PRODUCT

We will use the MagPro X100 system (MagVenture Inc., Alpharetta, Georgia, USA) for transcranial magnetic stimulation. The MagPro X100 is an advanced, high performance magnetic stimulator designed primarily for research purposes. It is a high-quality tool for researchers with a large choice of stimulating parameters and has stimulation rates up to 100 pulses per second at high intensities and the possibility to combine waveforms and pulse modes.

The simulator has several features:

- 3 waveforms: Biphasic, Biphasic Burst and Monophasic.
- Selectable current direction.
- Stimulation rates up to 100 pulses per second.
- Easily connects to external equipment via programmable input/output triggers.
- System operation control via a built-in computer, eliminating the need for an external computer to set up and control the timing of stimulus sequences.
- Controllable from an external device.

7.1 SAFETY FEATURES

In the USA, federal law regulates the sale of Medical Devices through the US Food and Drug Administration (FDA). This is done to ensure safety and effectiveness. Devices which are permitted to be marketed for their intended use must either have a 510(k) or PMA clearance.
MagPro® stimulators R20, R30, R30 with MagOption, X100, and X100 with MagOption are all FDA 510(k) cleared (k160280, k061645, k091940 and k150641).

k150641: The intended use is treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.
k160280, k061645, k091940: The intended use is for stimulation of peripheral nerves for diagnostic purposes.
The use of devices for other than their FDA cleared intended use is considered as investigational. Such use is only permitted if the Investigational Device Exemption (IDE) guidelines have been followed. For full information on this procedure, please consult FDA's website (www.fda.gov).
All investigational devices must be labeled in accordance with the labeling provisions of the IDE regulation (§ 812.5) and must bear a label with this statement:
"CAUTION Investigational Device. Limited by Federal (or United States) law to investigational use."

7.2 PREPARATION AND ADMINISTRATION OF STUDY INVESTIGATIONAL PRODUCT

After participants have completed the questionnaire, they will be comfortably seated. The researcher will be thoroughly trained in the safe use of TMS. All researchers administering TMS have written and digital documentation of training. Researchers will be present at all times during stimulation. To monitor side effects of stimulation, a questionnaire will be administered after each stimulation session.

7.3 ASSESSMENT OF PARTICIPANT COMPLIANCE WITH STUDY INVESTIGATIONAL PRODUCT

Compliance for this study is determined as completion of all five sessions.

8 POTENTIAL RISKS AND BENEFITS

8.1 BENEFITS TO PARTICIPANTS AND SOCIETY

This research has the potential to provide critical data for understanding the oscillatory dynamics that underlie output-gating. The current study has no immediate benefit to the healthy participants that participate. However, the results of this study may be used to develop novel tools for the treatment of psychiatric mood-disorders that involve a detriment in cognitive control. Furthermore, simultaneous neuro-imaging with brain stimulation will provide increased understanding of the neural mechanisms that underlie the efficacy of brain stimulation.

8.2 POTENTIAL RISKS

8.2.1 PSYCHOLOGICAL

Risk of Embarrassment: Self-report questionnaire contains questions regarding personal information. This risk is necessary in order to assess symptomology and associated psychopathology. Participants will be assured upon intake that only study personnel will see any answers.

Risk of Confidentiality Breach. To avoid breaches in confidentiality, study documents that contain personal information, including the informed consent, and the document that links study ID numbers to personal identifying information are kept in locked filing cabinets in locked rooms, separate from any source documents containing participating dummy identifiers. All data is stored in locked cabinets inside locked offices; electronic data will be stored only on password-protected computers, and data encryption methods will be used during communication between investigators. Only study personnel will have access to these data. All study staff participate in annual human participating training that includes education about responsibilities to minimize the risk of confidentiality breach. In the unlikely event of a breach of confidentiality, people might discover that an individual was involved in this research study and some people might not agree with the principle of participating in research or of changing natural brain activity.

Risk of Claustrophobia: There is an additional psychological aspect in that some participants may become claustrophobic upon entering the small space of the MRI bore. Participants are screened for claustrophobia

to prevent this risk. To reduce psychological distress, participants are informed that they can withdraw consent and stop participation at any time. Participants are monitored throughout the MRI scans and can terminate the scan at any time by squeezing a ball held in the hand.

8.2.1 PHYSICAL

Risk of Injury and Discomfort: Transcranial magnetic stimulation has been cleared for use in the USA by the FDA. TMS (the methodology used in this experiment) has nothing to do with electroconvulsive therapy that applies many orders of magnitude higher stimulation current. The level of electrical stimulation produced by TMS is within the range of activity that is endogenous to the brain. Furthermore, the intensity of stimulation is calibrated to the sensitivity of the individual participant such that the level of stimulation is matched to that of naturally occurring activity. In order to monitor side-effects, we will be administering an adverse effects stimulation questionnaire after each stimulation session to determine whether these effects were experienced. Research personnel present during these sessions will also check with the participant periodically during the stimulation to see whether they are comfortable. If any side-effect occurs that is rated by the participant and confirmed by the researcher to be stronger than "moderate," the stimulation will be immediately stopped.

Risk of Hearing Loss: There is a theoretical risk that TMS may damage hearing over prolonged exposure given the proximity of the stimulator to the ears (Rossi, Hallett et al. 2009, Rossi, Antal et al. 2020). Thus, we provide participants with ear plugs during motor threshold stimulation and with EEG-compatible ear-buds with an inflatable foam shape during task performance with TMS. These ear buds provide noise protection by making a tight seal and contain a small tube so that we can play white noise to the participant to help mask the noise of the stimulation for analysis purposes. In addition, the experimenter wears ear plugs during TMS to protect their hearing.

Risk of Injury from Magnetic Resonance Imaging (MRI): MRI will be conducted within the Biomedical Research Imaging Center (BRIC) at UNC Chapel Hill. The BRIC has a full-time staff that is well trained in the safety involved with MRI. Participants complete a contraindications form for MRI upon enrollment in each study. Any questions or concerns from the researcher can be addressed by the staff at the BRIC. In addition, the participant completes an additional screening form in the presence of the staff at the BRIC to further ensure that all safety concerns are addressed. The specific risks that are presented to the participant are avoided by effective screening. These risks include physical injury from the presence of metal within the body or in the environment when entering the magnetic field of the MRI. The strong magnetic field will pull metal towards the center of the field. Thus, it is imperative that all metal is removed from the body and any participants with metal within the body do not enter the field. The MR technicians at the BRIC maintain strict boundaries and screening via metal detector before entering rooms near to the MRI, adjacent to the MRI room, and the MRI room. This three-staged system is standard practice for MRI. Participants are provided with a medical gown and private changing room within the BRIC. This ensures that there is no chance that participants will enter the room with metallic objects in their pockets (e.g. phones or wallet). In addition, technicians screen participants and walk through a check list. Another risk from the MRI is the chance of a skin burn from clothing that contains metallic microfibers/particles. Thus, participants wear a medical gown to avoid the complication from modern athletic clothing technology. These risks are well-understood by the scientific community and extensive safety procedures are put in place by regulatory oversight that are maintained by the BRIC.

8.3 REFERRALS FOR MEDICAL FOLLOW-UP OR PSYCHOLOGICAL COUNSELING

There is a theoretical likelihood that stimulation of neuronal circuits can lead to epileptic discharge. To minimize this occurrence, we screen and exclude participants with personal and family history of neurological conditions from the study. If abnormalities or a seizure is witnessed during the course of the study, a referral will be made to the UNC Department of Neurology for follow-up. In the theoretical event that a seizure is witnessed that involves the loss of consciousness, the participants will be told not to operate a motor vehicle until cleared by the DMV.

To ensure participant comfort, a researcher will periodically check in with the participant about any side-effects he/she may be experiencing during each stimulation session. Following the conclusion of the stimulation session, the participant will receive an Adverse Effects Questionnaire to report on any of the side-effects he/she may have experienced. This questionnaire reports side-effects on a Likert scale (1=Absent, 2=Mild, 3=Moderate, 4=Severe). If the participant reports side-effects of Severe intensity, a researcher will discuss the side-effects with the participant at that time and note this response in an adverse events form (Appendix B). Depending on the expert judgement of the principal investigator, the adverse event will be determined to be mild, moderate, or severe and recorded in the adverse events log (Appendix D).

8.3.1 INCIDENTAL FINDINGS FROM MRI

When imaging the brain there is a chance that the MRI scan will reveal a neurological irregularity that might be of medical importance to the participant. These incidental findings are uncommon and rarely lead to early identification of neurological issues. However, as is standard practice, we allow participants the option to choose to be alerted to any incidental findings. In the consent form, participant can opt out of being notified about incidental findings. If a researcher notices a neurological abnormality, then they will reach out to our collaborators in the department of neurology to investigate the MRI scan further. If the neurologist considers the abnormality to be of medical importance, then the participant will be contacted for future steps. It should be noted that the research MRI scans used (T1-weighted) are not diagnostic scans and are not sensitive to detecting common neurological problems such as brain cancer. There is no expectation that the participant population studied in this research program will be of greater likelihood for incidental finding.

8.3.2 PREGNANCY FOLLOW-UP

Pregnancy tests will be administered on the first session of the experiment to all female participants to confirm that the participant is not pregnant. On subsequent sessions, female participants will be asked if it is possible that they may have become pregnant since the previous session. If the participant responds yes, or is unsure, then a pregnancy test will be administered. If a participant becomes pregnant during the course of the study, she will be withdrawn from further participation. There are no plans to follow-up with participants who become pregnant while enrolled in the study.

9 DATA AND SAFETY MONITORING

9.1 FROHLICH LAB MONITORING PLAN

The purpose of this monitoring plan is to present the Frohlich Lab's approach to monitoring clinical trials. The plan facilitates compliance with good clinical practice (GCP):

a. The rights and well-being of human participants are protected.
b. The reported trial data are accurate, complete, and verifiable from source documents
c. The conduct of the trial is in compliance with the currently approved protocol/amendment(s) with GCP, and with applicable regulatory requirement(s)

This section identifies key monitoring activities and specifies the data to be reviewed over the course of a clinical trial. This is a single site, investigator-initiated, clinical trial, so there will be no site monitoring plan in place.
The latest version of the approved IRB application for this clinical trial will be followed at all times. This responsibility falls into the hands of the researcher. If at any time there is a deviation from protocol, the deviation from protocol log will be filled out. All team members will be trained on how and when to use this log. The most up-to-date IRB application will be on file in the Clinical Trials office in Room 233 of the Medical School Wing C. Deviations will be sent to the IRB every 4-6 weeks (if necessary).
Periodically, study staff will review informed consent forms to ensure that (1) these forms have been filled out appropriately, and (2) the consent form process was followed and properly documented. Should any consent form be in violation, the research team will perform and document a complete review of all consent forms.
AE and SAE are clearly defined in this document. Documents of AE and SAE can be found in the study binder on file in the Clinical Trials office in Room 233 of the Medical School Wing C. It is the responsibility of the researcher to report all events to the PI in a timely manner. All AEs and SAEs will be discussed with the PI. For our practices, we have adapted the decision tree provided by the UNC-CH IRB to assist with reporting of such events.

9.2 SAFETY OVERSIGHT

Safety oversight will be under the direction of the PI, who will review AEs in real time and make decisions regarding a participant's continuation of the clinical trial.

There is a theoretical likelihood that stimulation of neuronal circuits can lead to epileptic discharge. To minimize this occurrence, we screen and exclude participants with personal and family history of neurological conditions from the study. Nonetheless, there is an extremely rate, but non-zero, chance that a seizure may occur.

1. Move the participant into a supine position if possible (the TMS chair can recline to achieve this position). Move everything away from the participant, so the participant cannot accidentally injure himself/herself while seizing. Do NOT try to restrain the participant or put things in the participant's mouth. Call 911 as soon as possible.
2. When the participant stops seizing, lay them on their right side with their head resting on their right arm.
3. When the participant is aware, explain that they had a seizure, which is a possible side effect of the study, but that having a seizure does not mean that they have epilepsy or will have long term changes in health/brain damage.
4. Wait for the EMTs to arrive. Call the medical monitor, Dr. Clio Rubios, and follow any instructions. Call the PI and inform them of the event.

If abnormalities or a seizure is witnessed during the course of the study, Dr. Clio Rubinos MD from the Department of Neurology will assist the participant in scheduling a follow-up appointment if she determines it to be necessary. In the theoretical event that a seizure is witnessed that involves the loss of consciousness, the participants will be told not to operate a motor vehicle until cleared by the DMV. All researchers are trained in First Aid which includes response to seizure. In addition, our TMS training module includes seizure response (see steps above). In the event of a seizure, a serious adverse event will be reported.
To ensure participant comfort, a researcher will periodically check in with the participant about any side-effects he/she may be experiencing during each stimulation session. Following the conclusion of the stimulation session, the participant will receive an Adverse Effects Questionnaire to report on any of the side-effects he/she may have experienced. This questionnaire reports side-effects on a Likert scale (1=Absent, 2=Mild, 3=Moderate, 4=Severe). If the participant reports side-effects of Severe intensity, a researcher will discuss the side-effects with the participant at that time and note this response in an adverse events form. Depending on the expert judgement of the principal

investigator, the adverse event will be determined to be mild, moderate, or severe and recorded in the adverse events log.

9.3 EARLY WITHDRAWAL OF PARTICIPANTS

9.3.1 REASONS FOR WITHDRAWAL

A study participant will be discontinued from further participation if:

- The participant meets any exclusion criteria (either newly developed or not previously recognized).
- Anything that, in the opinion of the investigator, would place the participant at increased risk or preclude the participant's full compliance with or completion of the study.

Participants are free to withdraw from participation in the study at any time upon request.

9.3.2 DATA COLLECTION FOR WITHDRAWN PARTICIPANTS

We will collect safety data on any participant discontinued because of an AE or SAE. In any case, every effort will be made to undertake protocol-specific follow-up procedures. If voluntary withdrawal occurs, the participant will be asked to continue scheduled evaluations and complete an end-of-study evaluation. If an AE has been reported, researchers will help the participant seek the medical care they need and a follow-up will be performed by the PI In the case of an early withdrawal, the researcher will make a note to file indicating this.

9.4 TERMINATION OF STUDY

If a seizure occurs at the time of a study visit, a temporary hold will be placed over the study and further investigation will ensue. This could lead to stopping the study prematurely or continuing on with further safety measures in place. If two seizures are witnessed during the study visits, the entire study will be stopped prematurely. These individuals will be referred for further medical attention. It is unlikely that a seizure will occur.

The study will also be stopped (at least temporarily) if studies provide evidence that transcranial magnetic stimulation caused brain damage or other harmful effects on participants, either short-term or long-term. Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.

The IRB will also be informed promptly and provided the reason(s) for the termination of suspension of by the investigator, as specified by the applicable regulatory requirement(s).

10 SAFETY & REPORTING

It is important to assess safety over the course of this study. This section describes in detail how safety is assessed, reporting of Adverse Events, Serious Adverse Events, and Unanticipated Problems. This section is a reference for internal use.

10.1 SAFETY PARAMETERS

STIMULATION SIDE EFFECTS. A stimulation adverse effects questionnaire used in previous studies will be administered at the end of each stimulation. This questionnaire will be used as a safety measure and to collect data on participant experience. The adverse effects questionnaire asks participants to respond on a 4-point Likert scale on the severity of symptoms experienced during the stimulation session (1 = absent, 2 = mild, 3 = moderate, 4 = severe). The side effects listed are headache, neck pain, scalp pain, tingling, itching, ringing/buzzing noise, burning sensation, local redness, sleepiness, trouble concentrating, improved mood, worsening of mood, dizziness, flickering lights, and

other (specify). Participants are also asked to rate on a 5-point Likert scale how related they believe the side effects to be to stimulation (1 = no relation, 2 = remote, 3 = possible, 4 = probable, 5 = definite).

10.2 METHODS AND TIMING FOR ASSESSING, RECORDING, AND ANALYZING SAFETY PARAMETERS

10.2.1 ADVERSE EVENTS

All AEs, including local and systemic reactions not meeting the criteria for "serious adverse events", will be captured on the appropriate CRF. In addition, the AE Report Form will be completed by the researcher (Appendix B). The AE Report Form includes the following:

- What is known about the stimulation
- What is known about previous reported side effects
- If the AE occurred in temporal relation to the stimulation
- Whether or not the AE improves or disappears when stimulation is stopped
- Whether the AE is worsening of baseline symptoms
- Whether the AE is related to concurrent medical condition or medication use

Once complete, this form will be given to the PI, who will review, comment, and sign this form. Completed forms will be placed in the participant's folder.

In addition, the researcher will document any AE occurrence on the AE log (*Appendix D*), which includes information such as the date of the AE, severity, relationship to the treatment (assessed by the PI*), actions taken, and outcome(s). The log will be reviewed and initialed by the PI within 10 work days after being completed. All AEs will be followed to adequate resolution and will be graded for severity and relationship to study. Any medical condition noted at the stimulation session will be considered at baseline and not reported as an AE.

***Relationship to Study Products**: The PI will determine whether an AE is associated with the study treatment. The event will be labeled associated if the event is temporally related to the administration of a therapy and no other factors can explain the event. The event will be labeled as not associated if the event is temporally independent of the study treatment and can be explained by external factors, such as major life events.

10.2.1 SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE): An SAE, as defined by the NIH, consists of adverse events that result in death, require either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, result in a persistent or significant disability/incapacity or result in congenital anomaly/birth defect. Other important medical events, based upon appropriate medical judgment, may also be considered Serious Adverse Events if a trial participant's health is at risk and intervention is required to prevent an outcome mentioned. Importantly, an SAE is any event of this kind that occurs within the time frame of study participation without any direct relationship to the study intervention itself.

All SAEs will be recorded on the Serious Adverse Events Form (Appendix B), documented in the UE/SAE log and reported to the IRB. The SAE Form will be completed by the researcher, and includes information relating to the onset and nature of the SAE, relationship to the study treatment, seriousness of the SAE, treatment required as a response to the SAE, and outcome. This form will be filed in the participant's folder at the resolution of the event. The researcher will complete the UE/SAE log (Appendix D) which includes information such as the date of the event, time at which the study team was informed of the event, details, when the IRB was notified, and the date that the SAE form was completed.

10.2.2 UNANTICIPATED PROBLEMS

Unexpected Events (UE) will be recorded on the UE/SAE log (Appendix D) and will include information such as the date of the event, when the study team was informed of this event, details of the event, when the IRB was notified, and whether the SAE form was completed. The IRB will be notified of each UE that may occur during the study.

The Office for Human Research Protections (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 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 (in the guidance document, 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.

If an UE occurs the IRB will be notified and the study will be adjusted as needed to protect the health and safety of the participants. Depending on the nature of the UE, the research protocol, inclusion/exclusion criteria, and informed consent will be changed to reflect the possibility of this event reoccurring. During this time, no new participants will be recruited and the research procedures for currently enrolled participants will be stopped. Each UE will be recorded and reported throughout the study.

10.3 REPORTING PROCEDURES

We will be adopting the following table for reporting procedures:

What Event is Reported	When is Event Reported	By Whom the Event is Reported	To Whom the Event is Reported
Fatal or life-threatening unexpected, suspected serious adverse reactions	Within **24 hours** of initial receipt of information	Investigator	Local/internal IRBs
Non-fatal, non-life threatening unexpected, suspected serious adverse reactions	Within **10 working days** of initial receipt of information	Researcher	Local/internal IRBs/Institutional Officials, DSMB
Unanticipated adverse device effects	Within **10 working days** of investigator first learning of effect	Investigator	Local/internal IRBs
Unanticipated problem that is not an SAE	Within **10 working days** of the investigator becoming aware of the problem	Investigator	Local/internal IRBs/Institutional officials
All Unanticipated Problems	Within **30 working days** of the IRB's receipt of the report of the UP from the investigator	IRB	OHRP
		Investigator	External IRBs

11.3.1 REPORTING OF PREGNANCY

Pregnancy tests will be administered on the first session of the experiment to all women of child-bearing potential (CBP). After testing negative, the experiment can continue. On subsequent sessions, female participants will be asked if it is possible that they may have become pregnant since the previous session. If the participant responds yes, or is unsure, then a pregnancy test will be administered. Within the study target population (ages 18-35), menstruating females, regardless of age are considered "CBP". Women who have had a hysterectomy or a bilateral oophorectomy are not considered of "CBP". There are no studies that suggest TMS would interfere with pregnancy. However, should a participant become pregnant during the study, her participation will be immediately terminated.

10.4 TYPES AND DURATION OF FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE EVENTS

Medical monitors and PI will follow up with participants within ten working days of an SAE that is related to stimulation.

11 STATISTICAL PLAN

The statistician for this study is Dr. Justin Riddle.

11.1 STATISTICAL ANALYSIS STRATEGIES

The statistical analysis plan below aligns with the aims that are described in Section 2.3. all statistical estimates of population parameters will be tabulated along with corresponding confidence intervals (CIs) to convey levels of precision / imprecision. All hypothesis tests that yield large p-values (p>0.05) will be reported as being inconclusive.

Phase One overarching goal: Investigate the causal role of frontal theta and parietal alpha oscillations in the prioritization and suppression of working memory representations. To control for non-specific effects of rhythmic TMS, we will use an active control: arrhythmic TMS (randomized inter-pulse-interval) that is matched to the target stimulation in number of pulses and temporal duration. All analyses will be performed on the difference from condition-matched arrhythmic TMS. The key analyses are built upon a three-way parallel arms design: with factors TMS frequency (theta versus alpha), location (frontal versus parietal), and cue direction (left versus right retro-cue). There is an equal number of trials for each of these conditions and there are 75 trials for each condition per participant.

Aim 1 (primary outcome): Stimulation that is aligned to the endogenous activity of the brain (frontal theta and parietal alpha) is hypothesized to improve performance whereas the mismatched frequency of stimulation is hypothesized to decrease performance (frontal alpha and parietal theta). Performance is assessed using Pashler's working memory capacity metric (k) which is defined as: $k = N * \frac{HR*FA}{1-FA}$ where N is the number of the items that are held in memory. HR is the hit rate defined as the percent correct for trials where the probe does not match the encoding array. FA is the false alarm rate defined as the percent incorrect for trials where the probe does match the encoding array. We will perform a two-way repeated-measures ANOVA with two within-participant factors TMS site (frontal or parietal) and TMS frequency (theta or alpha). We expert to observe a small p-value ($p < 0.05$) for the interaction between TMS site and TMS frequency. Post-hoc t-tests will be performed using Tukey's method to control for multiple comparisons. *Sensitivity analysis*: In addition to calculating changes in working memory capacity, the impact on hit rate, false alarm rate, and overall accuracy will be calculated. The robustness of these effects will be estimated using an individual differences analyses where baseline performance is used as a covariate to improve model estimation. Finally, the titration of working memory load by participant will be added as a covariate to explore if this factor changes the model estimation. These are framed as exploratory analyses.

Aim 2 (primary outcome): Stimulation is hypothesized to increase the targeted frequency of stimulation relative to arrhythmic stimulation. This aim will provide evidence of target engagement, i.e. that stimulation is effective at modulating the targeted rhythm. Using Morlet wavelet convolution, the amplitude of theta and alpha oscillations will be estimated during task performance. The average across trials for each conditions will be calculated and baseline corrected using decibels to the time before the encoding array (700 to 300 milliseconds). Then, the average amplitude within the individual theta (ITF +/- 1 Hz) and alpha frequency (IAF +/- 1 Hz) band will be calculated for the second half of the train of TMS pulses. Previous research has shown that amplitude increase from stimulation increases over the course of the TMS train. Frontal-theta and parietal-alpha amplitude values will be submitted to a two-way repeated-measures ANOVA with TMS frequency by TMS site. We hypothesize to find a significant interaction ($p < 0.05$) between TMS site and TMS frequency such that theta amplitude in frontal cortex increases greater for TMS to frontal in theta frequency and alpha amplitude in parietal cortex increases greater for TMS to parietal cortex in alpha frequency. Post-hoc t-tests will be performed using Tukey's method to control for multiple comparisons. *Sensitivity analysis*: To understand the specificity of this effect, the time-course for the impact of stimulation of amplitude will be plotted as well as the topographic plot for our effects. Cluster analysis will be used to estimate the spread of our effect in time and space. These analyses provide evidence to the robustness of the

impact of stimulation on amplitude.

Aim 3 (secondary outcome): Theta and alpha oscillations are hypothesized to play antagonistic roles whereby theta oscillations are associated with an increase in neural excitability and alpha oscillations are associated with a decrease in neural excitability. Therefore, we will investigate the impact of stimulation on the other frequency band. Theta stimulation is hypothesized to decrease the amplitude of alpha oscillations and alpha stimulation is hypothesized to decrease theta oscillations. This method is identical for that of Aim 2 except that the value submitted to the ANOVA are instead frontal-alpha and parietal-theta amplitude values. We hypothesize to find a significant interaction ($p < 0.05$) between TMS site and TMS frequency such that alpha amplitude decrease is greater for TMS to frontal in theta frequency and theta amplitude decrease is greater for TMS to parietal cortex in alpha frequency. Post-hoc t-tests will be performed using Tukey's method to control for multiple comparisons. *Sensitivity analysis*: Similar to the sensitivity analysis of Aim 2, the time-course and topographic plots with cluster analysis will quantify the spread of these effects. Furthermore, an exploratory theta-alpha antagonism metric (theta amplitude minus alpha amplitude within the site of interest) will be used to quantify a shift in the relative distribution of theta and alpha amplitude.

Aim 4 (secondary outcome): Theta oscillations in frontal cortex are hypothesized to play a causal role in precision of working memory representations. During the probe, the participant responds with a specific color from a comprehensive color wheel. Plus or minus 15 degrees around the color wheel is considered "correct." For the correct trials, the precision is calculated as the distance in degrees from the response of the participant to the actual color of the memory item. To investigate if theta oscillations play a causal role in precision, the impact of theta stimulation on precision relative to arrhythmic and as a function of visual field will be investigated using a two-way repeated-measures ANOVA: TMS frequency (theta or alpha) and visual field (left and right) for stimulation to frontal cortex. We hypothesize to find an interaction between TMS frequency and visual field such that precision is increased when theta stimulation is applied to the frontal cortex with a retro-cue to the contralateral visual field (right visual field). Post-hoc t-tests will be performed using Tukey's method to control for multiple comparisons. *Sensitivity analysis*: To better understand the impact of stimulation on precision, we will include addition covariates such as the location in the color space and the accuracy for the participant across color space. It is possible that participants will have differences in sensitivity to color changes dependent on the color, so this control analyses accounts for those differences.

Aim 5 (secondary outcome): Stimulation that is aligned to the endogenous activity of the brain is hypothesized to entrain neural activity. Inter-trial phase coherence (ITPC) quantifies alignment of neural oscillations across trials. Stimulation in frontal-theta and parietal-alpha is proposed to increase ITPC in a frequency specific manner relative to control stimulation. A similar method for extracting instantaneous phase is used as that used to extract instantaneous amplitude (Aim 2). ITPC is calculated as the average phase angle in complex space of unit vectors across trials, then taking the magnitude of the resulting vector. These ITPC values are then averaged for the second half of the TMS train as described in (Aim 2). Frontal-theta and parietal-alpha ITPC values will be submitted to a two-way repeated-measures ANOVA with TMS frequency by TMS site. We hypothesize to find a significant interaction ($p < 0.05$) between TMS site and TMS frequency such that theta ITPC in frontal cortex increases greater for TMS to frontal in theta frequency and alpha ITPC in parietal cortex increases greater for TMS to parietal cortex in alpha frequency. Post-hoc t-tests will be performed using Tukey's method to control for multiple comparisons. *Sensitivity analysis*: Similar to the sensitivity analysis of Aim 2, the time-course and topographic plots with cluster analysis will quantify the spread of these effects.

Phase Two Overarching Goal: Investigate the causal role of in-phase theta-frequency between frontal and parietal cortex in the prioritization and suppression of working memory representations. To control for non-specific effects of dual-site rhythmic TMS, we will use an active control: arrhythmic TMS (randomized inter-pulse-interval). Two

forms of arrhythmic stimulation are used: arrhythmic-in-synchrony stimulation delivers simultaneous stimulation to the two sites, but there is no consistent frequency component to the stimulation. Thus, activity in the two sites may be synchronized but not in a frequency-specific manner. The second control condition for stimulation is arrhythmic-independent where two trains of TMS are delivered in random patterns. There is no synchronization between the two pulse trains. Arrhythmic-independent controls for frequency and synchrony specificity of stimulation. All analyses will be performed on the difference from condition-matched arrhythmic TMS (in-phase minus arrhythmic-in-synchrony and anti-phase minus arrhythmic-independent). The key analyses are built upon a three-way design: with factors TMS frequency (theta and alpha), TMS alignment (in-phase and anti-phase), and cue direction (left and right retro-cue).

Aim 6 (primary outcome): Stimulation that is delivered in-phase to frontal and parietal cortex in the theta frequency is hypothesized to increased working memory capacity relative to anti-phase theta stimulation. Working memory capacity is quantified using Pashler's metric (see Aim 1). We will perform a two-way repeated-measures ANOVA with a between participants factor of TMS frequency (theta and alpha) and within-participants factor of TMS alignment (in-phase and anti-phase). We hypothesize to find a significant interaction ($p < 0.05$) between TMS frequency and TMS alignment such that in-phase TMS in theta-frequency increases working memory capacity. Post-hoc t-tests will be performed using Tukey's method to control for multiple comparisons. *Sensitivity analysis*: Similar to aim 1, the impact of stimulation on hit rate, false alarm rate, and overall accuracy will be calculated. The robustness of these effects will be estimated using an individual differences analyses where baseline performance is used as a covariate to improve model estimation. Finally, the titration of working memory load by participant will be added as a covariate to explore if this factor changes the model estimation. These are framed as exploratory analyses.

Aim 7 (primary outcome): Stimulation that is delivered in-phase to frontal and parietal cortex in theta frequency is hypothesized to increase functional connectivity between the regions in a frequency specific manner. Functional connectivity will be measured using weighted phase lag index (WPLI). To calculate WPLI, first Morlet wavelet convolution is performed to extract instantaneous phase and amplitude for the frequency of interest for the two target sites. Next, the cross-spectral density is calculated (one signal multiplied by the complex conjugate of the other). From the cross-spectral density the imaginary component of the resulting signal is extracted. Then those imaginary values are averaged over the time frame of instance (here, the second half of the stimulation train). Finally, the magnitude of the resulting vector is taken to be the WPLI. This metric quantifies the consistency of phase lag between the two target regions and is weighted towards signals with a 90 or 270 degree offset to address a common confound in EEG, volume conduction. We hypothesize that in-phase theta-frequency stimulation will increase theta-frequency WPLI strength between frontal and parietal cortex. In addition, we hypothesize that in-phase theta frequency stimulation will increase WPLI magnitude for retro-cues to the right visual field greater than the increase for stimulation with a retro-cue to the left visual field. This hypothesis is motivated by the finding that the left hemisphere processes information for the contralateral visual hemifield and that theta oscillations are linked to the active processing of information. Using a two-way ANOVA with factors for TMS frequency (theta or alpha) and retro-cue direction (left or right), we hypothesize a significant interaction ($p < 0.05$) between TMS frequency and retro-cue direction such that WPLI magnitude is the greatest for theta-frequency stimulation with a retro-cue to the right visual field. Post-hoc t-tests will be performed using Tukey's method to control for multiple comparisons. *Sensitivity analysis*: The frequency, topographic, and spatial specificity of these effects will be explored. Similar to Aim 2, the time-course of WPLI can be estimated using a sliding window to demonstrate if functional connectivity rises and peaks at the end of the stimulation train. Furthermore, the topographic increase in functional connectivity will be quantified across the scalp to see if the effect is specific to the targeted regions. Finally, the frequency specificity will be explored by calculating functional connectivity across the full spectral range (2-30 Hz) and the specificity of connectivity changes in frequency domain will be displayed. Together, these analyses will establish the robustness

of our a priori effect. Furthermore, these confirmatory sensitivity analyses avoid the multiple comparisons problem by relying on the initially established analyses.

Aim 8 (secondary outcome): Stimulation that is delivered in-phase is hypothesized to decrease the relative phase difference (phase lag) between the frontal and parietal cortex, whereas anti-phase stimulation is hypothesized to increase the phase lag. If stimulation entrained neural activity directly to the stimulation train, then this pattern of phase lag differences would be expected (because in-phase stimulation is delivered with zero phase lag and anti-phase stimulation is delivered with a phase lag). To calculate phase lag, first Morlet wavelet convolution is performed to extract instantaneous phase and amplitude for the frequency of interest for the two target sites. Next, the cross-spectral density is calculated (one signal multiplied by the complex conjugate of the other). From the cross-spectral density the phase angle is extracted, this is the phase lag. Then those phase lag values are averaged over the time frame of instance (here, the second half of the stimulation train). Finally, the angle of the resulting vector is taken to be the average phase lag. This metric quantifies the degrees of phase lag between the two target regions. Using a two-way ANOVA with factors for TMS frequency (theta or alpha) and TMS alignment (in-phase or anti-phase), we hypothesize a significant main effect ($p < 0.05$) of TMS alignment such that phase lag is different between in-phase and anti-phase where in-phase decreases the phase lag and anti-phase increases the phase lag. We also hypothesize that this effect will be strongest for theta-frequency stimulation, which is hypothesized to be revealed as a significant main effect between TMS frequency and TMS alignment. Post-hoc t-tests will be performed using Tukey's method to control for multiple comparisons. *Sensitivity analysis*: Similar to Aim 7, the spread of stimulation effects in time, space, and frequency will be explored.

11.2 SAMPLE SIZE RATIONALE

Based on a previous study with the current behavioral paradigm and similar TMS manipulation, the effect size of the interaction between TMS site and TMS frequency on WM capacity was 0.532 and used 21 participants. A power analysis of this effect suggests that to reach 95% statistical power we would need to recruit 48 participants. Therefore, we will perform our final analysis on 48 participants. Previous studies using a similar methodology of concurrent rhythmic TMS and EEG to look for changes in oscillatory power of the frequency of rhythmic TMS have used 10 participants for alpha frequency TMS (Thut et al., 2011) and 17 participants for theta rhythmic TMS (Albouy et al. 2017). Here, we propose to collect 48 participants. Therefore, our statistical power exceeds that of previous studies published in high-impact journals using a nearly identical methodology. Furthermore, we utilize a repeated-measures inter-mixed design in order to maximize our ability to control for confounding variables and increase statistical power. Based on a previous study by Thut et al., 2011 that found an increase in alpha oscillatory power from alpha rhythmic TMS relative to arrhythmic TMS with an effect size of 0.83 and 10 participants, we would need 21 participants to reach 95% statistical power for this comparison. Based on a previous study by Albouy et al., 2017 that found an increase in theta oscillatory power from theta rhythmic TMS relative to arrhythmic TMS with an effect size of 0.56 and 17 participants, we would need 44 participants to reach 95% statistical power for this comparison. Therefore, we estimate that based on these previously reported effect sizes for the impact of rhythmic TMS on behavior and oscillatory power measured by EEG in similar studies and our proposed sample size of 48 participants, we conclude that the proposed study has sufficient statistical power to answer the posed hypotheses.

It should be noted that our experimental design improves upon previous designs by sufficiently powering our "small n," of the number of trials per condition (Nee 2019). This factor is often overlooked in many power analyses. For the proposed experimental design, 75 trials per condition ensures that we have sufficient power at the level of each participant. The number of trials is critical to increasing the precision of each estimated metric for each participant. Some analyses of statistical power have found that this aspect is sometimes more important than the number of

participants. We maximize our statistical power by using a large number of trials for each participant and by using a large number of participants, relative to standard sample and trial sizes in the literature.

11.3 DATA MANAGEMENT

Data will be stored in a password-protected cloud-based data system that does not contain any participant information. Individual records are referred to by dummy identifiers that cannot be traced back to the study participants except with the master code list that is stored separately in a secured location.

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed participant authorization informing the participant of the following:

-What protected health information (PHI) will be collected from the participants in this study

-Who will have access to that information and why

-Who will use or disclose that information

-The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the participant is alive) at the end of their scheduled study period.

The responsibilities designated to each member of the research team are documented on the Delegation of Authority Form. The researcher will be responsible for the informed consent process, review for eligibility, questionnaire administration, data entry, device administration, EEG administration, and CRF entries. The researcher will be responsible for AE/SAE documentation and reporting, while the PI will be responsible for the AE assessment, review of the AE documentation forms, and overview of the research staff.

All data (including AEs, concomitant medications, and expected adverse reactions data) will be entered into a data capture system provided by REDCap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

All assessments completed by the participant at home will be completed via REDCap as well, ensuring participant security and confidentiality.

All deviations from the protocol will be addressed in study participant source documents. The researcher will complete a Protocol Deviation Log using the participant code as the identifier. This form will collect information such as the date the deviation occurred, details of what the deviation consisted of, any corrective and preventative actions that were taken as a result of the deviation, and the date that the PI and IRB were notified. The PI will review the information and initial once approved. A completed copy of the Protocol Deviation Form will be maintained in the regulatory file, as well as in the participant's source document. Protocol deviations will be sent to the IRB per their guidelines. The site PI/study staff will be responsible for knowing and adhering to their IRB requirements.

According to the University of North Carolina at Chapel Hill's Archives and Record Management Services schedule for General Records Retention and Disposition Schedule 6.10, records will be kept for 5 years after the completion of the study or grant end date, whichever is later.

12 DATA HANDLING AND RECORD KEEPING

The researchers are responsible for the accuracy, completeness, legibility, and timeliness of the data reported.

12.1 PHI AND HIPAA

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed participant authorization informing the participant of the following:

- What protected health information (PHI) will be collected from the participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the participant is alive) at the end of their scheduled study period.

12.2 CONFIDENTIALITY

12.2.1 ACCESS TO SOURCE DOCUMENTS

The researchers and PI will have access to all of the source documents collected over the course of the study. The medical monitor will have access to files upon request, as they will need access to the locked filing cabinets and rooms in which these documents are located.

Data will stay on a password-protected computer. Subsequently, a copy will be processed on a separate, password-protected desktop computer in the Frohlich Lab (Neuroscience Research Building 4129).

12.2.3 OTHER

Please note that there is no significant risk of deductive disclosure in this study. In addition, none of the groupings or subgroupings used in analysis will be small enough to allow individuals to be identified.

12.3 SOURCE DOCUMENTS

Source data is all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source data include:

PARTNERS HUMAN RESEARCH COMMITTEE (IRB).

- All IRB correspondences are documented
- The study staff is IRB approved prior to performing any study procedures
- Adverse events and deviations are reported to the IRB per current guidelines and stored appropriately
- All versions of the IRB protocols and informed consent forms are on file

INFORMED CONSENT.

- Ensure that participant identification is not recorded on the ICF (i.e., no participant ID)
- There is documentation that the participant is given a copy of the consent form
- The participant and study representative signed and dated the consent form for him/herself
- The participant initialed and dated all appropriate pages on the informed consent form
- Note to file (Appendix F) made for any informed consent deviations

- Ensure a valid (current version date) copy of the consent form was used

PROTOCOL DEVIATIONS.

- Any and all protocol deviations (exceptions and violations) are documented in the participant folder and reported to the IRB as required

OTHER SOURCE DOCUMENTS.

- Each participant folder will contain a checklist to ensure that all source documents are administered and collected properly. The checklist will be dated by the researcher for each time an assessment is administered
- Review participant folders to ensure the accuracy, completeness, and legibility of the data.
- Any correction made to the source documents is dated, initialed, and explained. The original entry should not be obscured.
- The protocol-specific source documents are on file.
- Source documents are completed in ink.
- Note to files (Appendix F) are made for missing or incomplete data and to explain any discrepancies or additional comments. The reason for missing data will be explained here.

12.4 DATA MANAGEMENT RESPONSIBILITIES

The responsibilities designated to each member of the research team are documented on the Delegation of Authority Form. The researcher will be responsible for the informed consent process, review for eligibility, questionnaire administration, data entry, device administration, EEG administration, and CRF entries. The researcher will be responsible for AE/SAE documentation and reporting, while the PI will be responsible for the AE assessment, review of the AE documentation forms, and overview of the research staff.

12.5 DATA CAPTURE METHODS (REDCAP)

All data (including AEs, concomitant medications, and expected adverse reactions data) will be entered into a data capture system provided by REDCap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

All assessments completed by the participant at home will be completed via REDCap as well, ensuring participant security and confidentiality.

12.6 PROTOCOL DEVIATIONS

All deviations from the protocol will be addressed in study participant source documents. The researcher will complete a Protocol Deviation Log using the participant code as the identifier. This form will collect information such as the date the deviation occurred, details of what the deviation consisted of, any corrective and preventative actions that were taken as a result of the deviation, and the date that the PI and IRB were notified. The PI will review the information and initial once approved. A completed copy of the Protocol Deviation Form will be maintained in the regulatory file, as well as in the participant's source document. Protocol deviations will be sent to the IRB per their guidelines. The site PI/study staff will be responsible for knowing and adhering to their IRB requirements.

12.7 RECORD RETENTION

According to the University of North Carolina at Chapel Hill's Archives and Record Management Services schedule for General Records Retention and Disposition Schedule 6.10, records will be kept for 5 years after the completion of the study or grant end date, whichever is later.

13 ETHICAL CONSIDERATIONS

13.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with the principles set forth in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

13.2 INSTITUTIONAL REVIEW BOARD (IRB)

The Office of Human Research Ethics is responsible for ethical and regulatory oversight of research at UNC-Chapel Hill that involves human participants. The OHRE administers, supports, and guides the work of the Institutional Review Boards and all related activities. Any research involving human participants proposed by faculty, staff, or students must be reviewed and approved by an IRB before research may begin, and before related grants may be funded. OHRE and the IRBs are critical components of the coordinated Human Research Protection Program, which serves to protect the rights and welfare of human participants. All components of this program must work together to ensure institutional compliance with ethical principles and regulatory requirements. The following is a mission statement for the coordinated Human Research Protection Program:

The University of North Carolina at Chapel Hill is committed to expanding and disseminating knowledge for the benefit of the people of North Carolina and the world. An important part of that commitment to knowledge is research of the highest quality on all aspects of the health and behavior of people, and such research is only possible through the participation of humans as research participants. Human participants are partners in research and a precious resource to the university. At UNC-Chapel Hill, human participant research is a privilege, but not a right. Consistent with that philosophy, it is the mission of the UNC-Chapel Hill Human Research Protection Program to ensure that:

a. The rights and welfare of human participants are paramount in the research process;
b. The highest standards of ethical conduct are employed in all research involving human participants;
c. Research investigators are properly trained in the ethical and regulatory aspects of research with human participants;
d. Research investigators deal honestly and fairly with human participants, informing them fully of procedures to be followed, and the risks and benefits of participating in research; and
e. Research using human participants at UNC-CH conforms to applicable local, state, and federal laws and regulations and the policies of the university.

13.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of TMS will be provided to the participants and their families. Consent forms describing, in detail, the study intervention, device, procedures, and risks are given to the participant and written documentation of informed consent is required prior to the administration of any treatment or assessments used in this study. All consent forms will be IRB-approved and updated with any new information as modifications are made throughout the study.

Together, the researcher and potential participants will review the study in its entirety by reviewing the consent form together in a private location. At several intervals during the consent review, the researcher will ask the participant questions that will assess the comprehension of the information in the consent. If the participant is unsure or does not know, the researcher will return to that section and more carefully explain the information. Participants must sign the informed consent document prior to any procedures taking place. If needed, the participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 EXCLUSION OF WOMEN, MINORITIES, AND CHILDREN (SPECIAL POPULATIONS)

Individuals that do not speak English are excluded because the ability to accurately and complete communicate study information, answer questions about the study, and obtain consent is necessary. Pregnant participants will be excluded despite the fact that theoretical risk to mother or fetus is exceedingly small, since no safety data for pregnancy is known to exist for transcranial magnetic/electrical stimulation studies.

13.5 PARTICIPANT CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the research team. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants.

All data will only be referenced by dummy identifier code. Data will be stored on a password protected computer. A key connecting names and code numbers will be kept in a locked cabinet, accessible only by research personnel. All data will be stored and analyzed on password protected computers, also only accessible by research personnel. Participants will not be identified in any report or publication about this study. See *10 Data Handling and Record Keeping* for more information on source documentation storage and security.

13.6 STUDY DISCONTINUATION

In the event that the study is discontinued, participants who have completed or who are still enrolled in the study will be notified. Any new information gained during the course of the study that might affect participant's willingness to continue will be communicated within 2 days of the PI learning this information.

14 PUBLICATION POLICY

There are no restrictions on publications since this is an investigator-initiated study funded by a grant agency that has no influence on the publications resulting from this study.

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APPENDIX A: SCHEDULE OF EVENTS

Procedures	Telephone Screening Interview	Session 1: Screening	Session 2: Baseline	Session 3: MRI	Sessions 4 & 5: Stimulation* (see footnote)
Provide Verbal Consent	x				
Signed Consent Form		x			
Assessment of Eligibility Criteria	x	x			
Urine Pregnancy Test		x			
Baseline Self-Report Assessments		x			
MRI contraindications				x	
Structural & resting-state MRI				x	
Resting-state with EEG			x		
Working memory task		x			
Working memory task with EEG			x		x
Working memory task with fMRI				x	
Stimulation contraindication check					x
Stimulation during task					x
Post-stimulation assessment					x

*For phase 1: stimulation is delivered to frontal or parietal cortex in sessions 4 and 5. In both sessions, stimulation is delivered in theta, alpha, or arrhythmic.

*For phase 2: stimulation is delivered to both frontal and parietal cortex with two stimulators. For session 4 and 5, Stimulation is delivered in either theta frequency or alpha frquency. In both sessions, stimulation is delievered in-phase, anti-phase, in-phase-arrhythmic, or independent-arrhythmic.

APPENDIX B: AE REPORT FORM

Adverse Effects Report:

Reasons for Report (adverse event, time, date and place of occurrence if available):

1. What do we already know about the stimulation?
    a.
2. What is the temporal relationship of the AE to the stimulation?
    a.
3. Does the AE improve or disappear when the stimulation is stopped?
    a.
4. Is the AE a worsening of baseline symptom(s)?
    a.
5. Is the AE a result of an underlying concurrent medical condition(s) or concurrent medication(s)?
    a.
6. Additional Information provided by research team
    a.

Research team member signature _____ Date_____

Co-Investigator:

_____
_____
_____
_____
_____

Steps to be taken (if applicable)

_____
_____
_____
_____

Co-I signature _____Date_____

PI Comments:

_____
_____
_____
_____
_____

Steps to be taken (if applicable)

_____
_____
_____
_____

PI signature _____Date_____

APPENDIX C: IRB AMENDMENT TRACKING LOG

Change Initiated By:		Description of IRB: Type and Brief Summary	Date Submitted to IRB	Date of IRB Response	Requires Stipulations? (Y/N)	Requires Updated Consent Form? (Y/N)	Stipulation Submission Date	IRB Approval Date
Initials	Reference ID							

APPENDIX D: AE REPORT FORM

Participant ID	**√ if AE meets definition of serious***	**Grade/Intensity** 1. Asymptomatic 2. Mild 3. Moderate 4. Severe	**Date of Incident**	**Relationship to study device** 1. Related 2. Possibly 3. Not Likely 4. Not Related	**Was Action Taken?**	**Action(s) Taken:**	**Outcome:** **1. Recovered** **2. Not Recovered** **3. Recovered w/Sequel** **4. Fatal** **5. Unknown**	**PI Initials / Date**
					Yes / No			
					Yes / No			
					Yes / No			
					Yes / No			
					Yes / No			
					Yes / No			
					Yes / No			
					Yes / No			
					Yes / No			
					Yes / No			

APPENDIX E: INFORMED CONSENT QUIZ

Name of Research Study:

You have been asked to be in a research study. This sheet will help you think of questions to ask but you may have other questions. This is not a test. We want to be sure you understand what it means to be in this research study. You should understand the research before you decide whether or not to participate.

1. What is the purpose of the research?

2. What are the possible benefits of the research?

3. What are the possible risks of the research?

4. Will everyone receive the same treatment?

5. How is this research different than the care or treatment I would get if I wasn't in the research study?

6. Does in the research cost me anything extra?

7. Can you stop being in the research once you've started?

8. Who will view your medical records?

9. Who do you call if I have questions about being a research participant?

10. Any questions?

APPENDIX F: NOTE TO FILE

IRB#: XX-XXXX PI: Flavio Frohlich

Study Title: [Insert Short Name]

Researcher: _____ Date of Occurrence: _____

Participant ID: _____

Reason for Note:

_____

_____

Note:

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Corrective action (if applicable):

_____

_____

_____

Signature: _____ Date: _____

APPENDIX G: TELEPHONE SCRIPT

Telephone Consent and Screening (TMSEEG)

Date: _____ ParticipantID: _____ Criteria fulfilled: ❒ Yes ❒ No

Hello, my name is _____. I'm calling in regards to your interest in our study on the effects of brain stimulation on brain activity. Do you have about 10 minutes now to hear about the study, answer a few screening questions, and possibly schedule your visit?

(If 'No', ask for a good time to call back)
(If 'Yes', proceed)

First, I need to ask for your verbal consent to conduct the screening interview. I will ask questions about your age, medication and drug use, and family and personal health history. You may decline to answer any questions, but please keep in mind that this may affect our ability to determine if you qualify for the study. Of course, the information you provide is strictly confidential, and will not be used for any purpose other than eligibility. Do you consent to participate in the screening interview?

(If 'No', thank them for their time and hang up.)
(If 'Yes', proceed)

Great! This study is looking at how brain activity responds to magnetic stimulation. In this study, a magnetic field will be applied to your scalp. Some participants have reported mild muscle twitching and headache, but no other side effects have been found. It is not a shock and should not cause pain.

This study will include five sessions scheduled at your convenience, each lasting approximately 1-3 hours. You will be compensated for your time after each session, with total compensation amounting to $170. We will ask that you maintain a regular sleep schedule during the study, and adhere to restrictions on alcohol consumption the day prior to each session. Are you still interested in participating?

(If 'No', thank them for their time)
(If 'Yes', proceed)

Great! In order to make sure you're eligible for the study, I need to ask you a few questions. Please answer yes, no, I do not know, or I prefer not to answer. If you are not sure what the question is asking please ask for clarification. You do not need to provide any details in your answer.

Age:_____ Sex:_____

---

1. Have you ever had a serious illness/accident that required hospitalization? Are you currently receiving any medical treatment?	❒ No	❒ Yes
2. Have you ever had suffered from a brain disease (e.g. epilepsy) or concussion?	❒ No	❒ Yes
3. Have you ever been diagnosed with a learning disability or ADD/ADHD?	❒ No	❒ Yes
4. Do you suffer from a mental/psychiatric disease, such as depression or schizophrenia?	❒ No	❒ Yes
5. Is there any family history of mental/psychiatric diseases?	❒ No	❒ Yes
6. Do you consume any elicit drugs, such as cannabis?	❒ No	❒ Yes
7. Is there any chance that you are pregnant or could become pregnant during the course of the study? (If female) Please note that we will also administer a pregnancy test at the start of every stimulation session if you answer yes or are unsure.	❒ No	❒ Yes
8. Do you have any implanted electronic devices?	❒ No	❒ Yes
Study obligations		
1. Do you think you can comply with all the study duties, which include maintaining a regular sleep schedule, and no caffeine, alcohol, or excessive exercise the day before or of a session?	❒ No	❒ Yes

Keeping in mind sessions last about 3 hours, what days and times work best for you?

APPENDIX H: MRI SCREENING FORM

MRI Screening Form

Magnetic Resonance Imaging (MRI) uses a powerful magnetic field to produce very clear images of the human body. When you are in the scan room any metallic objects on or within your body could be affected by the magnetic field. Therefore, all individuals are required to fill out this form before entering the MR environment or MR system room. Be advised, the MR system magnet is ALWAYS on.

Your Name: _____Date of Birth: _____ Weight: _____ Height: _____ Gender (check one):☐Male ☐Female

Please indicate by checking yes or no for each of the following:
Have you ever had a surgical procedure or operation of any kind? ☐ ☐

If yes, please list all operations and give approximate dates:
_____
_____
_____

Have you ever worked as a machinist, grinder, welder, or have you
ever had an injury to the eye involving a metallic object? ☐ ☐ If yes, please describe:

_____

Have you ever been injured by a metallic foreign body ☐ ☐ (bullet, BB, shrapnel etc.)? If yes, please describe:

_____

Remove all metallic objects before entering the MR environment or MR system room including hearing aids, beeper, cell phone, keys, eyeglasses, hair pins, barrettes, jewelry (including body piercing jewelry), watch, safety pins, paperclips, money clip, credit cards, bank cards, magnetic strip cards, coins, pens, pocket knife, nail clipper, steel-toed boots/shoes, and tools. Loose metallic objects are especially prohibited in the MR system room and MR environment. Please consult the MRI Technologist or Radiologist if you have any question or concern BEFORE you enter the MR system room.

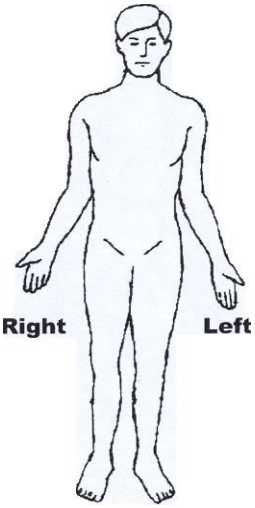
Some of the following items may be hazardous to your safety and some can interfere with the MRI examination. Please check the correct answer.

Do you have any of the following? ☐Yes ☐No

Cardiac pacemaker permanent retainers, or other dental implant
Implanted cardiac defibrillator Aneurysm clip(s)
Carotid artery vascular clamp Neurostimulator

Insulin or infusion pump
Implanted drug infusion device
Bone growth/fusion stimulator Cochlear, otologic, or ear implant
Any type of prosthesis (eye, penile, etc.) Artificial limb or joint
Electrodes (on body, head, or brain) Intravascular stents, filters, or coils
Shunt (spinal or intraventricular)
Swan-Ganz catheter
Any implant held in place by a magnet Transdermal delivery system (Nitro)IUD or diaphragm
Tattooed makeup (eyeliner, lips, etc.)
Body piercing(s), (Remove before MRI)
Any metal fragments
Internal pacing wires
Metal or wire mesh implants
Hearing aid (Remove before MRI)
Dentures (Remove before MRI), braces
Claustrophobia
Pregnancy or breastfeeding

Please mark on the figure below, the location of any implant or metal inside of or on your body.



Other, please explain:_____

Allergic reaction to MRI contrast agent Drug allergies, list:_____

As a safety precaution you, will be asked to change into clothing provided by BRIC MRI staff.

I the undersigned have answered the above questions accurately. I understand that all metallic objects including: jewelry, credit cards, eyeglasses, pins, watches, phones, pagers and dentures, must be removed prior to entering the MRI scan room. A secure location will be provided for my personal belongings.

Signature_____Date_____