CLINICAL RESEARCH PROTOCOL

INVESTIGATIONAL PRODUCT	Transcranial Magnetic Stimulation (TMS): *MagPro X100 Stimulator/ Cool-B65 Butterfly Coil/ MRI-B91 TMS Coil*
PROTOCOL TITLE	Individualized Closed Loop TMS for Working Memory Enhancement
IRB PROTOCOL NUMBER	832891
PRINCIPAL INVESTIGATOR	Desmond J. Oathes, PhD. Department of Psychiatry University of Pennsylvania
FUNDING SPONSOR(S)	National Institutes of Health (NIH)
PROTOCOL VERSION	V7.2 August 2023
DATED	September 8, 2023
CLINICALTRIALS.GOV NUMBER	NCT04402294

Protocol Details

Basic Info

Confirmation Number:	**djabjdjj**
Protocol Number:	**832891**
Created By:	**LYU, MENGQUN**
Principal Investigator:	**OATHES, DESMOND J**
Protocol Title:	**Optimizing Neuromodulation through Individualized Stimulation Frequencies**
Short Title:	**Individualized Loop TMS**
Protocol Description:	**Transcranial Magnetic Stimulation (TMS) is a non-invasive mechanism for stimulating the human brain. TMS can potentiate or inhibit activity in various brain regions, and it allows researchers to exert causal control over neural pathways. We will use real-time fMRI brain readout to optimize TMS delivery and measure changes in behavioral and brain response following the neuromodulation in healthy participants.**
Submission Type:	**Biomedical Research**
Application Type:	**EXPEDITED Category 1**

Study Personnel

Principal Investigator

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GCP Training Completed:	**Yes**
Training Expiration Date:	**06/05/2022**
Name of course completed :	**Good Clinical Practice: An Introduction to ICH (GCP) Guidelines**

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Name of course completed :	**CITI Good Clinical Practice (GCP) - OCR**

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Training Expiration Date:	
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**
GCP Training Completed:	**Yes**
Training Expiration Date:	**07/05/2025**
Name of course completed :	**Good Clinical Practice: An Introduction to ICH (GCP) Guidelines**

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Training Expiration Date:	
Name of course completed :	**CITI Protection of Human Subjects Research Training - ORA**
GCP Training Completed:	**Yes**
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Name of course completed :	**Good Clinical Practice: An Introduction to ICH (GCP) Guidelines**

Responsible Org (Department/School/Division):

10579 - PS-Center for the Neuroscience of Depression & Stress

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GCP Training Completed:	**No**
Training Expiration Date:	
Name of course completed:	

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Training Expiration Date:	
Name of course completed:	

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Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**
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Training Expiration Date:	**12/07/2024**
Name of course completed:	**Good Clinical Practice: An Introduction to ICH (GCP) Guidelines**
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HS Training Completed:	**Yes**
Training Expiration Date:	
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**
GCP Training Completed:	**Yes**
Training Expiration Date:	**06/21/2022**
Name of course completed:	**CITI Good Clinical Practice (GCP) - OCR**
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HS Training Completed:	**Yes**
Training Expiration Date:	
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**
GCP Training Completed:	**Yes**
Training Expiration Date:	**03/28/2026**
Name of course completed:	**CITI Good Clinical Practice (GCP) - OCR**
Name:	**HAMMETT, ETHAN C**
Department/School/Division:	**PS-Center for the Neuroscience of Depression & Stress**
HS Training Completed:	**Yes**
Training Expiration Date:	
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**
GCP Training Completed:	**Yes**
Training Expiration Date:	**06/20/2026**
Name of course completed:	**CITI Good Clinical Practice (GCP) - OCR**
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HS Training Completed:	**Yes**
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GCP Training Completed:	**No**
Training Expiration Date:	
Name of course completed:	

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HS Training Completed:	**Yes**
Training Expiration Date:	
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**
GCP Training Completed:	**Yes**
Training Expiration Date:	**06/10/2025**
Name of course completed:	**Good Clinical Practice: An Introduction to ICH (GCP) Guidelines**
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Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**
GCP Training Completed:	**Yes**
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Name of course completed:	**Good Clinical Practice: An Introduction to ICH (GCP) Guidelines**
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Training Expiration Date:	
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**
GCP Training Completed:	**Yes**
Training Expiration Date:	**12/04/2023**
Name of course completed:	**CITI Good Clinical Practice (GCP) - OCR**
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Department/School/Division:	**PS-Center for the Neuroscience of Depression & Stress**
HS Training Completed:	**Yes**
Training Expiration Date:	
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**
GCP Training Completed:	**Yes**
Training Expiration Date:	**06/12/2026**
Name of course completed:	**CITI Good Clinical Practice (GCP) - OCR**
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HS Training Completed:	**Yes**
Training Expiration Date:	
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**
GCP Training Completed:	**No**
Training Expiration Date:	
Name of course completed:	

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HS Training Completed:	**Yes**
Training Expiration Date:	
Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**
GCP Training Completed:	**Yes**
Training Expiration Date:	**10/09/2023**
Name of course completed:	**Good Clinical Practice: An Introduction to ICH (GCP) Guidelines**

Disclosure of Significant Financial Interests*
Does any person who is responsible for the design, conduct, or reporting of this research protocol have a **FINANCIAL INTEREST**?
No

Penn Intellectual Property*
To the best of the Principal Investigator's knowledge, does this protocol involve the testing, development or evaluation of a drug, device, product, or other type of intellectual property (IP) that is owned by or assigned to the University of Pennsylvania?
No

Certification
I have reviewed the *Financial Disclosure and Presumptively Prohibited Conflicts for Faculty Participating in Clinical Trials* and the *Financial Disclosure Policy for Research and Sponsored Projects* with all persons who are responsible for the design, conduct, or reporting of this research; and all required Disclosures have been attached to this application.
Yes

Biomedical Research

Clinical Trial*
Is this a clinical trial? Please note the following definition:Clinical trial is defined as a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. See CFR 45.46.102(b)
Yes

If Yes, please be aware that for each clinical trial conducted or supported by a Federal department or agency, one IRB-approved informed consent form used to enroll subjects must be posted by the awardee or the Federal department or agency component conducting the trial on a publicly available Federal Web site that will be established as a repository for such informed consent forms. For more guidance, please see: https://irb.upenn.edu/homepage/how-to-submit/initial-submission/2018-common- rule. Please see: https://irb.upenn.edu/clinicaltrials for additional clinical trial requirements.

Investigator Initiated Trial*
Is this an investigator initiated trial? Please select "Yes" if ALL the following conditions are met:The research is subject to FDA regulations for human subjects research.The individual PI both initiates (plans and designs) and conducts an investigation and under whose immediate direction the investigational agent is administered or dispensed. The individual investigator has absolute responsibility and accountability and designs, conducts, monitors, manages the data, prepares reports and oversees all regulatory and ethical matters. See 21 CFR 312.3
Yes

If Yes, please be aware that the investigator may be required to create and manage a record of this trial in https://clinicaltrials.gov.

Drugs or Devices*
Does this research study involve Drugs or Devices?
Yes: Investigational devices that may qualify as Non-Significant Risk.

IND Exemption

For studies that fall under an IND exemption, please provide the number below

For studies including IND or IDE's, please provide the number(s) below

IDE Review*
NOTE: For research involving investigational devices, you are required to review the guidance on Managing Research Device Inventory. Consult the Penn Manual for Clinical Research: https://www.med.upenn.edu/pennmanual/secure/investigational-product-management-at-sites-not-using-investigational-drug-services-(ids).html Please check the box Yes if you have reviewed the guidance.
Yes

Research Device Management*
Please indicate how research device(s) will be managed.
The device receipt, storage and dispensing is being conducted by the research team (please provide information in the protocol summary as to how this will be conducted)

Drug, Herbal Product or Other Chemical Element Management *
Please indicate how drugs, herbal products or other chemical entities will be managed.
Not Applicable (no drugs, herbal products or other chemical entities)

Radiation Exposure*
Are research subjects receiving any radiation exposure solely because they are enrolled in this protocol? (e.g. X-rays, CT, Fluoroscopy, DEXA, pQCT, FDG, Tc-99m, etc.)?IF YES, the protocol must be approved by the RRSC (Radiation Research Safety Committee). Consult EHRS web site: www.ehrs.upenn.edu/protocols/radiohuman.html for more information.If you have questions, email jjesik@ehrs.upenn.edu or kavyap@upenn.eduIf your protocol includes Nuclear Medicine Procedures, the protocol must be reviewed by the Nuclear Med Operations Committee: https://redcap.link/NMOPS
No

Gene Transfer*
Does this research involve gene transfer (including all vectors) to human subjects? IF YES, the protocol must be approved by the Institutional Biosafety Committee. Consult EHRS web site: www.ehrs.upenn.edu/protocols/bio_humans.html for submission requirements If you have questions, call 215-898-4453. The protocol may also require review by the Senior Vice Provost for Research's Human Research Advisory Committee(HRAC). The IRB will notify the PI and study staff if this review is warranted.
No

Human Source Material*
Does this research include collection or use of human source material (i.e., human blood, blood products, tissues or body fluids)? IF YES, consult the EHRS web site: www.ehrs.upenn.edu/programs/bio/bbpathogens.html for information on OSHA Bloodborne Pathogens requirements (training, vaccination, work practices and Exposure Control Plan). If you have questions, call 215-898-4453.
No

Image Guided Biopsies*
Does the research involve imaging guided biopsy? IF YES, please contact the Clinical Imaging Core. See https://www.med.upenn.edu/cbi for more details. Any questions should be directed to the Director of Research Operations, Dept of Radiology, Kathleen Thomas.
No

Computerized Tomography (CT) Studies*
Does the protocol involve CT scans that are not considered standard of care and are being performed for research purposes?IF YES, complete the CACTIS Committee Application: https://is.gd/CACTIS and consult CACTIS website: http://www.uphs.upenn.edu/radiology/research/labs/cactis/ for application requirements.
No

CAMRIS and MRI Studies*
Is an MRI scan being performed for research only and NOT considered standard of care (example: specific scanner, parameters or solely for the purposes of research)?NOTE: Research/non-standard use of MRI may include but is not limited to any of the following: Situations in which MRI results may impact subjects current clinical care plan or treatment decisions, such as:The study requires a customized report with specifics regarding the study protocol (i.e., specific measurements or details); Introduction of a device of any kind during the MRI that is not used during a 'standard of care' type scan.Your MRI is not consistent with standard care time points for MRI imaging.Your MRI is not paid for by insurance.IF YES, consult CAMRIS website: https://www.med.upenn.edu/camris/application- and-faq.html for application requirements and required institutional consent form language.
Yes

Investigational Agent or Device within the Operating Room*
Does the research project involve the use of an investigational agent or device within the Operating Room?
No

Cancer Related research not being conducted by an NCI cooperative group*
Does this protocol involve cancer-related studies in any of the following categories? Therapeutic, Prevention, Supportive Care, Screening, Early Detection, or Diagnostic, Epidemiologic, Observational, Outcome, Ancillary or Correlative. For a description of these categories, see http://www.ctsrmc.org/submitting_a_protocol.php NCI Cooperative Groups are as follows:Alliance for Clinical Trials in OncologyNCI Clinical Trials Group (Canadian Cancer Society) (NCCTG)Children's Oncology Group (COG)NRG Oncology GroupECOG-ACRIN Cancer Research GroupSouthwest Oncology Group (SWOG) IF YES, the protocol must be submitted to the Cancer Center's Clinical Trials Scientific Review Committee for scientific review and approval prior to obtaining IRB approval. Consult the CTSRMC website: www.ctsrmc.org for application requirements
No

Processing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)?
No

In-House Manufacturing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)?
No

HIPAA / Protected Health Information
Does the research proposal involve accessing (viewing / using), collecting, or disclosing of protected health information (PHI) directly from participants or their medical or dental record for research purposes?
Yes

Indicate which item is provided with this submission:

Modified research informed consent document that incorporates HIPAA requirements

Cohort/data analysis tools used

Remote Study Visits
Does the research proposal involve conducting research visits remotely via any type of video conferencing software?
Yes

Conference software used
Zoom

CHPS Resources*
Does the research involve CHPS resources?
No

HUP Inpatient Nursing Resources
Does this research include an inpatient admission at HUP?
No

Pathology and Laboratory Medicine Resources*
Will samples be collected by hospital phlebotomy and/or processed or analyzed by any of the clinical laboratories of the University of Pennsylvania Health System?
No

Research Involves Apheresis, Cell Collection, and/or Blood Product Collection*
Does this research involve collection of blood products in the Penn Donor Center and/or the use of apheresis for treatment or collection of cells or other blood components?
No

Research involving blood transfusion or drug infusions*
Will your research involve blood transfusion or infusion of study drug in 3 Ravdin Apheresis Unit for research purposes?
No

Trial in Radiation Oncology
Is this research a prospective trial being done in Radiation Oncology, and if so, has this protocol been approved by the Radiation Oncology Protocol committee?
N/A

Study in Radiation Oncology
Is this research a retrospective study being done in Radiation Oncology, and if so, has this project been reviewed by the Radiation Oncology Clinical Research Group?
N/A

Use of UPHS services*
Does your study require the use of University of Pennsylvania Health System (UPHS) services, tests or procedures , whether considered routine care or strictly for research purposes? (UPHS includes all Penn hospitals and clinical practices, including the Clinical Care Associates network of community practices). Examples of UPHS services/tests/procedures includes the Clinical Translational Research Center (CTRC), laboratory tests, use of the pathology lab, cardiovascular imaging tests or radiology imaging tests (whether being billed via the Service Center or through UPHS), other diagnostic tests &procedures and associated professional services, etc.
No

Veteran's Affairs (VA) Patients or Subjects
Does your study involve data from Veteran's Affairs (VA) patients or subjects?
No

If yes, was this approved by the Philadelphia VA?

No

Out of State Research
Will any Penn personnel conduct any research activities outside of the State of Pennsylvania?
No

Research involving Virtua Health
Will any Penn personnel conduct any research activities at a Virtua Health site location, OR in collaboration with Virtua Health System personnel, OR using any Virtua Health System resources (e.g.,

medical records)?
No

Primary Focus*
Other

Protocol Interventions

	Sociobehavioral (i.e. cognitive or behavioral therapy)
	Drug
	Device - therapeutic
	Device - diagnostic (assessing a device for sensitivity or specificity in disease diagnosis)
	Surgical
x	**Diagnostic test/procedure (research-related diagnostic test or procedure)**
	Obtaining human tissue for basic research or biospecimen bank
	Survey instrument
	None of the above

The following documents are currently attached to this item:

There are no documents attached for this item.

Sponsors

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Department budget code

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Funding Sponsors

Funding sponsors billing address
If you have selected a commercial or industry sponsor, please provide the appropriate address and contact information for the Sponsor for the purposes of billing for IRB review fees (initial review, continuing review and convened modification fees apply here). If the Sponsor is not industry/ commercial, this information is not necessary to provide with your application.

Funding sponsors gift
Is this research being funded by a philanthropic gift?

Regulatory Sponsor

IND Sponsor

none

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Industry Sponsor

None

Project Funding*
Is this project funded by or associated with a grant or contract?
Yes

Selected Proposals

Proposal No	**Title**
10070605	**Individualized Closed Loop TMS for Working Memory Enhancement**

Sponsor Funding
Is this study funded by an industry sponsor?
No

Status of contract

The following documents are currently attached to this item:

There are no documents attached for this item.

Multi-Center Research

Penn as lead
1. Is this a multi-center study where Penn is serving as the Lead Site or the Penn PI is serving as the Lead Investigator?
No

Management of Information for Multi-Center Research

Penn irb of record
2. Is this a multi-center study where the Penn IRB will be asked to serve as the IRB of Record for other external study sites?
No

Other Sites

No other sites

Protocol

Abstract
Transcranial magnetic stimulation (TMS) is a non-invasive mechanism for stimulating brain regions in humans. TMS can potentiate or inhibit activity in various brain regions, and it allows researchers to exert causal control to explore and define network connectivity among brain regions. Using real-time brain readouts combined with interleaved TMS/fMRI, we will compare the optimal and the least optimal stimulation frequency based on individualized functional connectivity networks. By comparing brain and behavioral changes after three days of neuromodulation at optimal and least optimal

stimulation frequency, we aim to explore whether optimal stimulation frequency will lead to more robust brain and behavior responses to repetitive TMS (rTMS).

Objectives

Overall objectives

We aim to evaluate whether optimized frequency (compared to the least-optimized frequency) of excitatory TMS will generate better results in behavior and brain activity among healthy participants. Specifically, we will develop a novel tool to compute individualized multi-scale functional connectivity networks using data from baseline resting and task-evoked brain states. Building on that, we will utilize recurrent neural networks (RNN) with long short-term memory (LSTM), a promising deep learning technique, to generate brain decoding models and obtain real-time readouts of brain states. We will then establish a closed loop of rTMS and brain readouts, fine-tuning the rTMS frequency to determine the optimal stimulation frequency for each participant. Participants will receive their optimal stimulation frequency of rTMS over a three-day neuromodulation session and their least optimal stimulation frequency (the frequency least successful in moving their brain state) over another three-day neuromodulation session (order counterbalanced across subjects). We hypothesize that optimal frequency will drive performance improvements and brain changes more than the least optimal frequency.

Primary outcome variable(s)

Behavior change (task performance) and brain activity change (in-scanner brain readouts during the working memory task or at rest) in response to neuromodulation.

Secondary outcome variable(s)

Correlation between changes in behavioral measures and changes in network connectivity before and after the neuromodulation.

Background

Repetitive TMS (rTMS) has been widely adopted to non-invasively stimulate the brain to improve working memory (WM) performance in both clinical and non-clinical samples (Brunoni & Vanderhasselt, 2014). However, behavioral and symptom responses to TMS remain heterogeneous and the factors governing the strength and direction of rTMS effects across individuals remain largely unknown. Accumulating evidence has demonstrated that TMS efficacy hinges upon the precision of TMS targeting, and individualized functional connectivity networks (FCNs) may help accurately identify TMS targets for individuals (Fox, Buckner, White, Greicius, & Pascual-Leone, 2012; Fox, Liu, & Pascual-Leone, 2013; Weigand et al., 2018) since effects of stimulation are propagated throughout both local and distributed brain networks (Herbsman et al., 2009; Kloppel et al., 2008). The functional brain state varies across individuals and within individuals over time (Bassett, Wymbs, Porter, Mucha, Carlson, & Grafton, 2011; Calhoun, Miller, Pearlson, & Adal, 2014; Finn, Scheinost, Finn, Shen, Papademetris, & Constable, 2017), which could substantially alter the impact of TMS. Preliminary research suggests that manipulating brain states during the delivery of repetitive TMS (rTMS) neuromodulation augments the behavioral impact of rTMS (Luber et al., 2017). Through manipulation of brain state with a related behavioral task and using fMRI as the feedback signal, it may be possible to tune rTMS delivery to maximally impact the desired brain states in awake behaving study participants in a highly individualized manner. Therefore, improved efficacy of TMS could be achieved through precise TMS targeting and optimal TMS delivery tailored for individuals and optimized online based on real-time readouts of brain states. FCNs derived from functional MRI have demonstrated promising performance for identification of reproducible individualized targets. However, existing methods are limited in that they typically identify group-level functional connectivity networks (FCNs) and focus on resting state fMRI alone. Our recent work suggests that individualized, sparse, non-negative FCNs provide enhanced ability for characterizing the functional brain of individual subjects (Li, Satterthwaite, & Fan, 2017). Moreover, recent evidence suggests that task fMRI can improve upon within-subject and between-subject estimates of stable brain network representations as compared with resting state fMRI only (Finn, Scheinost, Finn, Shen, Papademetris, & Constable, 2017). Based on these findings, current study will focus on both resting and task-evoked brain states and individualized, multiscale, hierarchical functional neuroanatomy, and we will extend upon our recent published work (Li et al., 2017, 2016; Li, Zhu, & Fan, 2018) using deep matrix decomposition techniques (Trigeorgis, Bousmalis, Zafeiriou, & Schuller, 2014; Zhao, Ding, & Fu, 2017). This strategy will yield a set of individualized FCNs that share similar spatial patterns across subjects at multiple scales with a hierarchical organization,

facilitating individualized precise TMS targeting. Another major innovation that will facilitate optimal TMS delivery is the brain decoding for real-time online brain readouts. Recent studies have demonstrated promising brain decoding performance of prediction models built upon functional connectivity measures among FCNs within time windows with a fixed width (Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012; Richiardi, Eryilmaz, Schwartz, Vuilleumier, & Van De Ville, 2011). However, such fixed time windows are not likely optimal over different brain states that change at unpredictable intervals. Meanwhile, recurrent neural networks (RNNs) with long short-term memory (LSTM) (Hochreiter & Schmidhuber, 1997) have achieved remarkable advances in sequence modeling (Lipton, Berkowitz, & Elkan, 2015), and these techniques have been successfully applied to EEG and ECoG data analysis (Glaser, Chowdhury, Perich, Miller, & Kording, 2017; Schwemmer et al., 2018). Our recent study has demonstrated that brain decoding models built upon individualized FCNs using LSTM RNNs accurately decode fine-grained WM tasks and motor tasks in real time (Li & Fan, 2018). Therefore, here we will build brain decoding models to obtain real-time readouts of brain states using LSTM RNNs. Besides TMS targeting, rTMS frequency has clear neurobiological consequences successfully measured in-vivo in non-human animal brains in a landmark study (Allen, Pasley, Duong, & Freeman, 2007). Our team has adopted the interleaved TMS/fMRI technique which will allow stimulation of specific nodes while recording fMRI responses from all other brain regions (Chen et al., 2013; Fonzo et al., 2001; Nahas et al., 2001). Building on this basic strategy and the innovative methodology mentioned above, we can fine-tune the TMS frequency based on real-time feedback of TMS induced effects on the brain. Specifically, we will target FCNs identified by a brain decoding model built using LSTM RNNs, apply short trains of in-scanner rTMS, monitor the resulting brain response with fMRI, and tune TMS delivery accordingly. As a result, we can optimize noninvasive brain stimulation through individualized target and frequency. By comparing behavioral and brain responses with optimized and non-optimized stimulation frequencies, this study will provide us novel insight to variability in response to TMS and will potentially enhance the capabilities of the existing device.

Study Design

Phase*
Not applicable

Design
This study will recruit 38 healthy participants, who will be recruited through the community via study advertisements. Prior to any study visits, all subjects will be pre-screened through a phone interview with a trained member of the study team or an online self-report screening, both through REDCap. The study involves 11 study visits. The first study visit will consist of a consenting and extended screening visit. All participants will have the opportunity to ask questions before signing the electronic consent form. We will complete a semi-structured clinical interview and will demonstrate TMS to ensure the participant is comfortable with all study procedures. This visit will be completed both remote and in- person. The second study visit will involve a 1-hour MRI scan. During the scan, the participant will complete multiple computerized tasks. The MRI scan will include both structural and functional scans, and those scans will be used to localize the stimulation target for the subsequent sessions. The third study visit will be a 2-hour TMS/fMRI session, and the participant will engage in behavioral tasks while interleaved rTMS rounds are delivered at different excitatory frequencies (frequency range: 2Hz-20Hz). This scan will be used to determine the optimal stimulation frequency for the individual participant. The fourth, fifth, and sixth study visits will involve neuromodulation with either the optimized frequency or the frequency least successful in moving a participants brain state, as determined from the third study visit. Each subject will receive ~3000 pulses in each session, including the pulses from the motor threshold determination. We will determine the adjusted MT by using the Stokes equation, which accounts for differences in cortical distance from the site relative to motor cortex (where the motor threshold is found). The stimulation amplitude will be equivalent to 110% of the adjusted MT. Prior studies have safely utilized TMS with such design (VanDerwerker et al., 2018; Cristancho, Trapp, Siddiqi, Dixon, & Lenze, 2018). The seventh study visit will involve a 1-hour TMS/fMRI session while the participant is engaging in a behavioral task.. This visit is designed to examine brain and behavioral changes after the first round of neuromodulation. The seventh and the eighth visit will be scheduled at least one week apart. The eighth, ninth, and tenth study visits will mirror the fourth, fifth, and sixth study visits and will involve neuromodulation with either the optimized or least-optimized individual frequency. The order of optimized and least-optimized frequencies will be counterbalanced across participants between Visit 4-6 and Visit 8-10 (i.e., half of the participants will receive stimulations of the two frequencies in one order, and the other half will receive stimulations of the two frequencies in the reverse order). The

eleventh visit will mirror the seventh visit and will examine brain and behavioral changes after the second round of neuromodulation.

Study duration
Each subject will spend a total of approximately 13.5-20 hours of participation in the study over 11 study sessions. The study schedule is as follows: Visit 1: Consent/Screening (1-3 hours) Visit 2: Baseline MRI (1.5-2 hours) Visit 3: TMS/fMRI (2-2.5 hours) Visit 4-6: 1st Neuromodulation Session (1-1.5 hours each) Visit 7: TMS/fMRI (1.5-2 hours) Visit 8-10: 2nd Neuromodulation Session (1-1.5 hours each) Visit 11: TMS/fMRI (1.5-2 hours).

Resources necessary for human research protection
Describe research staff and justify that the staff are adequate in number and qualifications to conduct the research. Describe how you will ensure that all staff assisting with the research are adequately informed about the protocol and their research related duties. Please allow adequate time for the researchers to conduct and complete the research. Please confirm that there are adequate facilities for the research.
Staff will be trained on the protocol and inclusion/exclusion criteria. TMS protocols will involve direct training with the Principal Investigator and the study physician, Ted Satterthwaite, M.D. Facilities will include Penn laboratory spaces specializing in advanced computing and analysis of neuroimaging and cognitive datasets. Scans will be conducted on a Siemens Prisma 3 Tesla whole-body MRI, housed in the Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS). Additional MRI resources, such as a mock scanner, may be accessed from the Center for Functional Neuroimaging (CfN).

Characteristics of the Study Population

Target population
38 healthy control participants to collect useable data from 28 healthy participants.

Subjects enrolled by Penn Researchers
38

Subjects enrolled by Collaborating Researchers
0

Accrual
All recruitment will be conducted through the University of Pennsylvania and the surrounding community to find a total of 38 healthy participants. It is assumed that there will be some participants who screen fail, are lost to follow up, withdraw, or complete without usable scanner data. Therefore, we estimate that we will need to consent/enroll up to 38 participants overall, in order to adequately test the hypotheses on at least 28 participants.

Key inclusion criteria
1)18-60 years old 2) Right handed 3) No psychiatric history as diagnosed by the SCID-V 4) Normal cognition 5) Capacity to give informed consent and follow study procedures 6) Sufficient command of English language to understand and respond to written as well as verbal instructions

Key exclusion criteria
1) History of neurological disorder or traumatic brain injury (other than mild) 2) Unable to have an MRI scan, or current or prior medical condition that could interfere with the collection or interpretation of MRI data 3) Unable to receive TMS 4) Implanted devices, such as an aneurysm clip or cardiac pacemaker 5) History of stroke, epilepsy, or brain scarring 6) Recent use of psychoactive medications, as determined by investigators 7) Pregnant, nursing, or trying to become pregnant (self-attestation alone) 8) Color blindness 9) Otherwise determined by investigator to be unfit for study

Vulnerable Populations

Children Form

Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus) Form

Fetuses and/or Neonates Form

Prisoners Form

Other

x **None of the above populations are included in the research study**

The following documents are currently attached to this item:

There are no documents attached for this item.

Populations vulnerable to undue influence or coercion

No subjects, including the economically disadvantaged, employees, and/or students at Penn, will be unduly influenced, encouraged, or coerced into participating in this study. These populations will not be targeted or excluded. If they are encountered and would like to participate, the appropriate measures will be taken in order to allow them the opportunity to provide consent.

Participant recruitment

Please describe the plan to equitably identify and recruit a diverse group of participants that is reflective of the population under study. If this is a multicenter protocol, the recruitment plan should describe the local (Penn) site's plan. Describe:how potential participants may be identified (review of medical records, Slicer Dicer, DAC reports including referrals from physician offices and clinics);who may approach potential participants;methods to achieve sample diversity and inclusiveness;what information may be presented to or discussed with them; andthe context and setting in which recruitment will happen.

All participants will be recruited through the University of Pennsylvania and the surrounding community. Subjects will be recruited through flyers, brochures, online advertising (CNDS website, Facebook, Craigslist, iConnect). All recruitment materials, including but not limited to flyers, brochures, referral letters, online postings, and email templates will be IRB-approved before distribution of any of these materials. Study coordinators may also contact participants from past studies at the CNDS who indicated they would be willing to be contacted about participating future studies at the center. Individuals will express interest by initiating contact with the research staff via phone or email for a phone-screening procedure or by completing an online screening form on REDCap. All subjects meeting basic inclusion criteria will be scheduled for a remote screening visit. In order to facilitate the enrollment of interested subjects in multiple studies, center-wide general pre- screening forms, phone screen and self-report screen will be used. The Center for Neuromodulation in Depression and Stress has numerous studies that all are closely related, in both purpose and eligibility criteria, a general pre-screening (both phone and self-report) has been created. Many participants will be eligible for multiple studies and will be presented with the opportunity to participate in all studies that they are eligible for. An additional benefit of a shared or general pre-screening is that participants who do not qualify for a specific study can be informed of other studies they are eligible for. It will be clearly explained to all individuals that this pre-screening is for multiple studies and that their information will be stored in REDCap (option given to have screening done on paper). Additionally, subjects will be recruited through Penn's Office of Clinical Research iConnect volunteer registry. Volunteers who have consented to be contacted regarding studies of interest will be sorted by relevant diagnoses and invited by study team members to fill out an online survey to determine eligibility.

Recruitment Materials

Is the research team using any recruitment materials? These may include but are not limited to: phone call scripts, radio/video scripts, flyers/brochures, internet postings, email, letters to potential participants, letters to patient physicians, My Penn Medicine (MPM), other direct messaging, etc. For guidance regarding recruitment materials, please review the IRB's guidance on Participant Recruitment Materials online:https://irb.upenn.edu/mission-institutional-review-board-irb/guidance

Yes

Use of Penn Media & Social Media Services
Will the recruitment plan propose to use any Penn media services (communications, marketing, etc.) for outreach via social media avenues (examples include: Facebook, Twitter, blogging, texting, etc.) or does the study team plan to directly use social media to recruit for the research?
Yes

Please identify which method(s) of social media you will utilize, the content of the text to be used, and the method(s) for posting this information (i.e., using Penn supported communication services). When proposing the text to utilize, please be aware of any social media limitations (i.e., number of characters allowed in a tweet) and any appropriate confidentiality practices necessary to be compliant with posting research recruitment text.NOTE: Penn Medicine must utilize one of the centralized PM Facebook Pages:ClinicalResearch@Penn Facebook pagePenn Medicine Facebook page@PennCancer Facebook pageAll clinical research paid Facebook ads must be listed on Clinical Research @ Penn Facebook page,www.facebook.com/ClinicalTrialsAtPenn. Exceptions to the above must get approval from the Penn Medicine Social Media Committee: pennmedicinesocialmediacommittee@uphs.upenn.edu.
We will post flyers and place brochures throughout the local community to recruit for this study. In addition, participants will be recruited through advertisements in print (e.g. local newspapers), online media/websites (e.g. craigslist.com, researchmatch.org, Penn Medicine, CNDS website, Facebook, and Google ads), as well as radio or TV ads. All recruitment materials, including but not limited to flyers, brochures, referral letters, online postings, and email templates will be IRB-approved before distribution of any of these materials.

The following documents are currently attached to this item:

Subject recruitment (03.15.2019_flyer_initialsubmission.docx)

Subject compensation*
Will subjects be financially compensated for their participation?
Yes

The following documents are currently attached to this item:

There are no documents attached for this item.

If there is subject compensation, provide the schedule for compensation per study visit or session and total amount for entire participation, either as text or separate document

Total compensation for completing all study visits is $720.00. Subjects will receive additional compensation ($0.17-$150) depending on the choices they make during the incentive-based tasks of the Neuromodulation Sessions. We will explain the details of the compensation before they begin the task. Subjects will receive compensation at the end of their study completion. If subjects do not fully complete the study, they will receive compensation for the parts of the study they did complete, based on the following outline: Visit 1: Clinical Interview ($20.00) Visit 2: Baseline MRI ($50.00) Visit 3 TMS/fMRI ($150.00) Visit 4-6: 1st Neuromodulation Session ($50.00 x 3 = $150.00) Visit 7: TMS/ fMRI ($100.00) Visit 8-10: 2nd Neuromodulation Session ($50.00 x 3 = $150.00) Visit 11: TMS/fMRI ($100.00). Subjects will be compensated through University of Pennsylvania supported Greenphire ClinCard. This is a reloadable virtual or physical prepaid card (similar to a debit/credit card) which allows funds to be available immediately. Study staff will provide participants with a ClinCard Cardholder FAQ: US document (attached). Subjects who do not feel comfortable with the Greenphire ClinCard may be compensated by a check, in lieu of the ClinCard. We are not stating this option in the ICF, as we would prefer all participants to use the ClinCard for consistency; however, we acknowledge that not all individuals will feel comfortable with this method and therefore, if a participant expresses discomfort, we will then verbally offer them the option of being paid with a check. If participants opt to have the payment provided to them in the form of a check; it will be mailed to their home address. Participants will be required to complete an electronic C-2 and a W-9, including providing their full social security number, in order to receive the study payment. If participants choose to participate in multiple studies at the center, some similar/identical study visits (mainly screening visit and baseline MRI) may not need to be repeated. If this is the case, participants will only be compensated for the new study procedures/visits they complete.

Study Procedures

Suicidal Ideation and Behavior

Does this research qualify as a clinical investigation that will utilize a test article (ie- drug or biological) which may carry a potential for central nervous system (CNS) effect(s)? Centeral nervous system(CNS) effect: the ability of a test article to enter into and potentially interact with the central nervoous system (brain and spinal cord). Clinical Investigation: Any experiment that involves a test article and one or more human subjects that either is subject to requirements for prior submission to the Food and Drug Adminstration (FDA) under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or is not subject to the requirements for prior submission to the FDA under these sections of the act, but, the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

No

Procedures

All participants will be recruited through the University of Pennsylvania and the surrounding community. Subjects will be pre-screened for eligibility through phone or online self-report screener in REDCap. Eligible subjects will be invited in for a screening visit. Visit 1 will be a consent/ screening session. This visit will involve remote and in-person procedures. During the remote visit, a coordinator will discuss the Informed Consent Form with the participant. After going through the ICF, participants will be asked to electronically sign at the end of the ICF and complete a Remote ICF Attestation form to ensure they understood all the procedures and risk associated with the study. If they agree to participate, they will complete questionnaires related to their medical history, demographics, and eligibility to receive MRI scans and TMS. After completing the questionnaires, participants will undergo a clinical interview. This interview could be done in person or remote. If participants meet eligibility for these initial procedures, we will schedule an in-person meeting to test TMS. For the TMS demo, participants will receive several short rounds of TMS test pulses to the prefrontal cortex to ensure comfort. During this demonstration we will identify the participants resting motor threshold (MT). MT is defined as the minimum magnetic flux needed to elicit a response in a target muscle in 5 out of 10 trials. MT is the standard in the field for measuring cortical excitability and to reduce seizure risk. While TMS is usually quite tolerable, a minority of participants (20%) cannot tolerate stimulation procedures. Screening data will be recorded in REDCap; this data will be retained indefinitely until the study enrollment is completed. The information collected in this initial visit will determine if the subject meets all inclusion criteria. If participants screen-fail or withdraw, we will assign the clinical interview compensation to their virtual Greenphire Clincard. Upon meeting all criteria for inclusion in the study, subjects will then return to complete a 1-hour baseline MRI scan at Visit 2. All MRI imaging protocols will be reviewed and approved by CAMRIS. An experienced technician and a member of the study team will be present during the MR session to ensure participant safety and well-being. If the participant complains of feeling claustrophobic and does not wish to complete the MRI, the study will be terminated. Emergency personnel and equipment are immediately available to the MRI room should the need arise. It is possible that during the course of the research study, the research staff may notice unexpected findings on an MRI scan. Should this occur, the findings will be assessed by a trained radiologist. The study doctor will inform research subjects of any significant findings. Visit 3 will include fMRI and interleaved TMS/fMRI. During this scan, the participant will perform a working memory N-back task several times. Brain data from the baseline MRI scan (stimulation target in individualized brain space) will be calibrated with the skin and scalp using a Polaris Vicra camera (Brainsight neuronavigation) to allow marking of the stimulation site on a swim cap for the TMS/fMRI session. During the MRI scan, participants will receive interleaved TMS/fMRI probes to the brain targets. The purpose of this TMS/fMRI scan is to probe and modulate and measure activity in targeted neural circuits following our established methods (Chen et al., 2013). Moreover, by building brain decoding models using LSTM RNNs deep-learning technique, we can establish a closed loop of rTMS and brain readouts. As a result, we will be able to fine-tune the rTMS frequency to achieve optimal brain state and maximized working memory performance during this session. Our MRI-compatible TMS system (MagPro X100 Stimulator, MRI-B91 TMS coil) is housed in Stellar Chance (SC3T) and the Hospital of the University of Pennsylvania (HUP 6) at the 3-Tesla MRI machine. The apparatus was installed under the supervision of Mark Elliott, Ph.D. a member of CAMRIS. TMS in an MRI scanner involves no additional risks to the subject. Visits 4-6 will involve excitatory rTMS delivered in the

same interleaved pattern at the same stimulation site as the TMS/fMRI session but with either the optimized frequency determined from that session or the frequency least successful in moving their brain state (half of the participants will receive optimized stimulation frequency, and the other half of the participants will receive least-optimized stimulation frequency during these sessions). The present study utilizes the same FDA-approved devices (Magventure Cool-Coil B65, MagVenture X100 Stimulator) to administer TMS. The TMS system is housed in the Richards Biomedical Building. Only individuals trained by the Principal Investigator (Desmond Oathes, Ph.D.) and, Ted Satterthwaite (M.D.) will dispense TMS. In addition to receiving TMS, participants will complete questionnaires and computerized tasks during these visits. The tasks will assess reaction time, working memory, decision- making. The decision-making task will be incentive-based and the amount the participant earns will be added to their final study compensation. During some of the tasks, we may ask subjects to wear a passive eye-tracking device to record the location of your gaze at any particular time. The order of tasks will be randomized for each participant. Visit 7 will involve a 1-hour TMS/fMRI session. Participants will complete the working memory N-back task while inside the scanner. The purpose of this visit is to examine the brain and behavioral changes after the first round of neuromodulation. Visit 8-10 will mirror Visit 4-6 and will involve neuromodulation with either the optimized or least-optimized individual frequency. The order of optimized and least-optimized frequencies will be counterbalanced across participants between Visit 4-6 and Visit 8-10 (i.e., half of the participants will receive stimulations of the two frequencies in one order, and the other half will receive stimulations of the two frequencies in the reverse order). Visit 7 and the Visit 8 will be scheduled at least one week apart.In addition, unless the MRI is unavailable or we encounter scheduling constrains, Visit #3-Visit #7 will be scheduled within the same work week, such as Visit #3 is on Monday, Visits #4-7 are Tuesday/ Wednesday/Thursday, respectively, and Visit #7 is on Friday. Similarly, Visit #8-Visit #10 will be scheduled 4 work-days in a row, either Monday-Thursday or Tuesday-Friday. Visit 11 will mirror Visit 7 and examine brain and behavioral changes after the second round of neuromodulation. Monitoring will include: (1) successful recruitment, retention; (2) subject adherence; (3) safety and tolerability.

The following documents are currently attached to this item:

There are no documents attached for this item.

Deception
Does your project use deception? Deception could be considered any direct misinformation presented to the subject or omission of key information pertaining to the design or nature of the project.
No

International Research
Are you conducting research outside of the United States?
No

Analysis Plan
For the primary within-subjects analyses, a time (pre vs post rTMS) by condition (optimized vs least-optimized frequency) ANOVA will be done both on task performance as well as fMRI voxelwise brain responses.

The following documents are currently attached to this item:

There are no documents attached for this item.

Data confidentiality

x **Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.**

x **Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.**

Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.

x **Wherever feasible, identifiers will be removed from study-related information.**

A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.

x **A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)**

x **Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.**

Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

Subject Confidentiality

Subjects entering the study will be given a unique identifying participant ID. Most data obtained will use this ID to remain de-identified. Any electronic forms (i.e., status log form) connecting the ID with the participant name will be stored in REDCap, a password protected, IRB compliant online databases, with identifier fields flagged for confidentiality. Any paper forms connecting the ID with the participant name (i.e., consent, MRI form) will be stored in secure cabinets inside locked rooms.

Sensitive Research Information*

Does this research involve collection of sensitive information about the subjects that should be excluded from the electronic medical record? [NOTE: This does not apply to: 1) research information that would not normally be included in the electronic medical record or 2) information that is in the electronic medical record as part of clinical care.]

No

Subject Privacy

Privacy refers to the person's desire to control access of others to themselves. Privacy concerns people, whereas confidentiality concerns data. Describe the strategies to protect privacy giving consideration to the following: The degree to which privacy can be expected in the proposed research and the safeguards that will be put into place to respect those boundaries. The methods used to identify and contact potential participants. The settings in which an individual will be interacting with an investigator. The privacy guidelines developed by relevant professions, professional associations and scholarly disciplines (e.g., psychiatry, genetic counseling, oral history, anthropology, psychology).

Participants will be recruited through the University of Pennsylvania, and surrounding community. When applicable, they will be identified and contacted through that facility. For future contact, they will be asked their preferred contact method. The study will be presented in a private room and the fMRI will also take place in a private room. All contact made with the participant will be done so when the coordinator(s) or investigator in private, as would be the case with a doctor making a call to their patient. Participants will further be informed & required to provide verbal consent to have their phone screen information (written consent within online self-report screener) retained in REDCap.

Disclosures

Will any data or specimens from Penn participants OR other research generated work product (e.g., intellectual property) be disclosed to any individuals, entities, or vendors, etc. outside of Penn?

No

Data Protection*

x **Name**

x **Street address, city, county, precinct, zip code, and equivalent geocodes**

x **All elements of dates (except year) for dates directly related to an individual and all ages over 89**

x **Telephone and fax number**

x **Electronic mail addresses**

x **Social security numbers**

Medical record numbers

Health plan ID numbers

Account numbers

Certificate/license numbers

Vehicle identifiers and serial numbers, including license plate numbers

Device identifiers/serial numbers

Web addresses (URLs)

Internet IP addresses

Biometric identifiers, incl. finger and voice prints

Full face photographic images and any comparable images

Any other unique identifying number, characteristic, or code

None

Does your research request both a waiver of HIPAA authorization for collection of patient information and involve providing Protected Health Information ("PHI") that is classified as a "limited data set" (city/town/state/zip code, dates except year, ages less than 90 or aggregate report for over 90) to a recipient outside of the University of Pennsylvania covered entity?
No

Tissue Specimens Obtained as Part of Research*
Are Tissue Specimens being obtained for research?
No

Tissue Specimens - Collected during regular care*
Will tissue specimens be collected during regulator clinical care (for treatment or diagnosis)?
No

Tissue Specimens - otherwise discarded*
Would specimens otherwise be discarded?
No

Tissue Specimens - publicly available*
Will tissue specimens be publicly available?
No

Tissue Specimens - Collected as part of research protocol*
Will tissue specimens be collected as part of the research protocol?
No

Tissue Specimens - Banking of blood, tissue etc. for future use*
Does research involve banking of blood, tissue, etc. for future use?
No

Genetic testing
If genetic testing is involved, describe the nature of the tests, including if the testing is predicative or exploratory in nature. If predictive, please describe plan for disclosing results to subjects and provision

of genetic counseling. Describe how subject confidentiality will be protected Note: If no genetic testing is to be obtained, write: "Not applicable."
Not applicable.

Consent

1. Consent Process

Overview
Consent will be obtained by a member of our research team. Because this study does not involve treatment, coercion is not a concern. Consent will be obtained remotely (via RedCap) where study staff members will discuss the Informed Consent Form, including the purpose of study, procedures, risks, and benefits. They will explain that participating is completely voluntary and that not participating will not change access to treatment in any way. The potential participant will be given the option to consider study enrollment and will not be forced to make a decision the same day. At the end of the ICF, there will be a HIPAA-compliant eSignature field following OCR- RedCap guidelines. By electronically signing the ICF they will be consenting to participate in the study. Enrolled participants will be asked to complete the Remote ICF Attestation Form to ensure they understood all the procedures and risks associated with the study. After the ICF process, we will begin the screening procedures. If the participant meets initial eligibility, they will be invited to an in-person meeting where we will provide a paper copy of the ICF on request. The patient will be reminded before and after enrolling, and before any research procedure that their participation is optional and has no impact on the care they can expect.

Children and Adolescents
N/A

Adult Subjects Not Competent to Give Consent
N/A - we are looking for cognitively normal participants, so all will have the competency to give consent.

2. Waiver of Consent

Waiver or Alteration of Informed Consent*
Waiver of written documentation of informed consent: the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context

Minimal Risk*

Impact on Subject Rights and Welfare*

Waiver Essential to Research*

Additional Information to Subjects

Written Statement of Research*
Yes

If no written statement will be provided, please provide justificiation

Request of waiver of documentation of informed consent for PRE-SCREENING activity only; phone and self-report screening will be captured via RedCap. Participants are informed of this and given the option to verbally consent; however, we will not be providing them a copy of this, as some individuals will not actually participate in the study and therefore the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality.

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit

Potential Study Risks

There is a small risk of loss of confidentiality. An exception to confidentiality is if a participant reports child abuse or neglect, or if they report suicidal or homicidal ideation or intent to the research team. Any information about child abuse or intent to harm oneself or others will be reported to authorities, as required by law. Clinical Interview and Assessment: Some discomfort may be associated with the clinical assessments conducted in this study. Participants may experience emotional discomfort when answering some questions in the questionnaires or when talking about personal information. Participants may choose not to answer any of the questions and to terminate their participation. MRI scan: Likely/Common: Subjects may experience claustrophobia (fear of enclosed spaces and/or anxious feelings accompanied by fast heart rate or shortness of breath) within the MRI scanner. In addition, the scanner produces a loud repetitive knocking noise during the study that some people find bothersome. If a subject has a problem with feeling uncomfortable while inside the scanner, they may stop this study. To lessen the noise, earplugs will be provided. Rare: Implanted medical devices and metallic foreign fragments inside the body may pose a risk if a subject were to enter the MRI magnet room. Devices such as Pacemakers, Internal Cardiac Defibrillators, Insulin Pumps, and other medical devices may also prevent a safe MRI. Therefore, questions regarding medical and work history will be asked prior to your exam. Patients who have metallic devices in their bodies will not be permitted to be scanned using MRI. There are no known risk factors associated with MRI scans for healthy subjects. Although there are no known risks related to MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no possible benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women. A MRI scan requires subjects to be in a partially enclosed space inside the scanner. Some people may find this to be uncomfortable and claustrophobic. Participants will be instructed to inform the doctor ordering the scan, or the study staff, if they suffer from claustrophobia. The MRI scanner produces different types of noises during a scan. Since the noise level can be loud, participants may be given special earplugs to reduce the noise. A MRI scanner has a strong magnet which attracts certain metals. If anyone has these types of metal in their body, the MRI's strong magnetic field can cause them to move which may cause injury. The MRI will not be performed on anyone having these types of metal in their body. To prevent an injury, participants will be asked questions or given a form requesting information about any metal in their body and if they work with metals. Some dyes in tattoos and permanent eyeliner contain metals which may move during the MRI scan causing the area with the tattoo to become irritated and swollen. No metal objects are allowed to be brought into the MRI scan room at any time, because the MRI magnet will quickly and strongly pull those items into the scanner. To prevent any injury to patients and staff and any damage to the MRI scanner, participants will be asked to remove all jewelry and clothing containing metal before you enter the MRI scan room. Also, since the MRI magnet will erase credit cards, they must not be taken into the scan room. Once participants are positioned in the scanner, the door to the room will be closed to prevent anyone with any metal object entering the scan room. TMS: TMS is considered to be a low-risk procedure. The most common side effect of TMS (approx 25% of patients) is a mild headache. Other side effects may include scalp discomfort at the site of stimulation and/ or muscle tenderness as a result of the TMS stimulation. They may also experience temporary and local bruising, swelling or pain from the swim cap and/ or muscle activation by TMS. This muscle activation may induce jaw or eyebrow movement during the TMS stimulation. If the TMS target is near the eye muscles, TMS stimulation may induce tear formation. Although studies have found no hearing impairments as a result of this sound, some subjects experience a mild temporary effect on their hearing. To minimize this possibility, subjects will be given protective earplugs. The most significant side effect associated with TMS is a TMS-induced seizure. However, in the most recent TMS safety guidelines (Rossi et. al, 2021), they show that a TMS-induced seizure in an individual without identifiable risks is very unlikely (1/100,000 sessions). Moreover, even though individuals with risk factors (history of epilepsy, brain lesion, brain scarring, or medication use) have a slightly higher risk of a TMS-induced seizure, the risk is still low (67/100,000 sessions). There are no known long-term adverse effects reported with the use of this device. There may be long-term risks due to TMS that are currently unknown. Rarely, device malfunction could result in a scalp burn. The effects of TMS on a fetus are unknown. Therefore, we require that females of child-bearing potential attest at the time of participation that they are not pregnant. TMS/fMRI: There is no added risk by performing TMS and fMRI together.

Potential Study Benefits
This study will provide no direct benefit to individual participants.

Alternatives to Participation (optional)
The alternative to participation is to not participate.

Data and Safety Monitoring
The PI will monitor the study for any serious and adverse events. All serious events (SAE) will be reported to the IRB: a) Death immediately b) Life-threating and all other SAEs within 7 calendar days. Should there be a serious event that occurs that increases the risks to the participants the study will be stopped, an investigation will be conducted, and a findings report will be generated before the study is resumed. Detailed Data Safety Monitoring Plan: This section describes the Data and Safety Monitoring Plan and quality assurance (QA) procedures that will be used for this proposed study. This monitoring plan details the frequency of monitoring visits, regulatory document review, and compliance review. Monitor Selection: One monitor will be assigned for this study and will be responsible to complete the monitoring process. The monitor will be a research coordinator at the center who is not the lead research coordinator for this study. An updated CV will be kept on file in the Research Personnel regulatory binder to document the qualifications of the monitor. The following activities will be completed by the monitor to close out the study: Ensure all data has been reviewed and collected; Confirm all reports of unanticipated problems have been reported to the IRB(s); Review the regulatory documentation and subject files for completeness and compliance with all applicable federal regulations; Ensure that all continuing review reports were submitted to and approved by the IRB(s); Review requirements for record retention with the investigator and the clinical staff. The checklist will be signed by the monitor and included in the regulatory files. Data Management: All data will be deidentified and only qualified research personnel will be having access. Records will be kept electronically on password protected servers. Safety Monitoring: All unanticipated problems will be reported to the Principal Investigator or delegated research staff for the duration of the study. The Principal Investigator has the front-line responsibility for identifying potential adverse events experienced by study participants, making adjustments accordingly, and reporting the experience. The P.I. is responsible for tracking these reports and relaying them as required to the IRBs and other investigators. Data integrity, safety, and privacy will be monitored by the PI and the coordinators.

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit Assessment
There is minimal risk from the research procedures (MRI, TMS, behavioral tasks). The potential benefit to society through the increased understanding of TMS far outweighs the potential risk from the MRI and TMS procedures. Additionally, those who would be unable to tolerate TMS or an MRI scan will be screened out.