PROTOCOL TITLE	Network Control TMS fMRI
IRB PROTOCOL NUMBER	830174
PRINCIPAL INVESTIGATOR	Desmond J. Oathes, PhD. Department of Psychiatry University of Pennsylvania
FUNDING SPONSOR(S)	National Institutes of Health
INVESTIGATIONAL PRODUCT	Transcranial magnetic stimulation (TMS) device that can stimulate brain regions noninvasively. • MagVenture X100 Stimulator • Cool-B65 Butterfly TMS Coil • MRI-B91 TMS Coil
PROTOCOL VERSION	V13
DATED	11/23/2022
CLINICALTRIALS.GOV NUMBER	NCT05736458

Basic Info

Protocol Number: :	**830174**
Principal Investigator:	**OATHES, DESMOND J**
Protocol Title:	**RF1: Network Control TMS fMRI**
Short Title:	**Network Control TMS fMRI**
Protocol Description:	**In a sample of healthy young adults and those with ADHD we will use diffusion imaging to create individualized TMS targets by identifying brain regions with high and low regional controllability. We will directly compare the brain network responses to TMS targeted to these regions using single-pulse TMS/fMRI recordings. We will also evaluate the impact of using TMS during a working memory task with the aim of enhancing both network responses to stimulation and the impact of TMS on behavior.**

Study Personnel

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

Responsible Org (Department/School/Division):

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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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HS Training Completed:	**Yes**
Training Expiration Date:	
Name of course completed:	**POR Recertification Quiz - Full Board Review - SOM**
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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Name of course completed:	**Good Clinical Practice: An Introduction to ICH (GCP) Guidelines**

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

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

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GCP Training Completed:	**Yes**
Training Expiration Date:	**12/04/2022**
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**
Training Expiration Date:	**08/04/2023**
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:	**02/18/2023**
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?
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.

Investigator Initiated Trial*
Is this an investigator initiated trial?
No

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 (e.g. X-rays, CT, Fluoroscopy, DEXA, pQCT, FDG, Tc-99m, etc.) that they would not receive if they were not enrolled in this protocol?
No

Gene Transfer*
Does this research involve gene transfer (including all vectors) to human subjects?
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)?
No

CACTIS and CT Studies*
Does the research involve Center for Advanced Computed Tomography Imaging Services (CACTIS) and CT studies that research subjects would not receive if they were not part of this protocol?
No

CAMRIS and MRI Studies*
Does the research involve Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS) and MRI studies that research subjects would not receive if they were not part of this protocol?
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?
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

Medical Information Disclosure*
Does the research proposal involve the use and disclosure of research subject's medical information for research purposes?

Yes

If the answer is YES, indicate which items is is provided with this submission:

Modified research informed consent document that incorporates HIPAA requirements

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?
Yes

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

Business Administrator

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Department budget code

000 - 000 - 0 - 000000 - 0000 - 0000 - 0000

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

Name:	**OATHES, DESMOND J**
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Does the IND Sponsor (or his or her spouse or dependent children) have a SIGNIFICANT FINANCIAL INTEREST, as defined above?
No

Industry Sponsor

None

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

Selected Proposals

Proposal No	**Title**
10064756-01	**Network Control and Functional Context: Mechanisms for TMS Response**

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) has evolved to become one of the most widely used approaches for non-invasive neuromodulation in humans and significant data suggests that it may improve working memory performance. This study explores the concept of applying TMS to specific targets during specific states which may enhance its impact on behavior. We hypothesize that appropriate stimulation within a specific working memory context will enhance both network responses to stimulation and the impact of TMS on behavior. In a sample of healthy adults and subset of young adults with ADHD, we will use diffusion imaging to create individualized TMS targets by identifying points in that brain that have high and low regional controllability. We will directly compare the brain network responses to TMS targeted to the high controllability and low controllability regions using single-pulse TMS/fMRI recordings. We will also evaluate the impact of using TMS to these regions during a working memory task (of both high and low memory load) with the aim of enhancing both network responses to stimulation and the impact of TMS on behavior. Participants will then receive repetitive TMS (rTMS) in the scanner to modulate these brain circuits. Following rTMS, we will re-interrogate the same circuit using single-pulse TMS/fMRI and participants will repeat the working memory task.

Objectives

Overall objectives
We will use ultra-high resolution diffusion spectrum imaging (DSI) to map the structural connectome and identify brain regions with high and low regional controllability. We will directly test whether TMS targeted to control points using network control theory on a single-subject basis results in greater network responses in single-pulse TMS/fMRI recordings. Specifically, we will vary the stimulation target in a counterbalanced order across two days of TMS/fMRI, where stimulation of a prefrontal control point (with high regional controllability) is compared with stimulation of a prefrontal region with low regional controllability. During each of these TMS/fMRI sessions, we will also evaluate the impact of functional context by stimulating under counterbalanced conditions of high or low working memory load. Critically, following these initial single-pulse experiments that interrogate network activation and interaction, each participant will receive rTMS in the scanner to modulate the system. We expect that rTMS targeted with network control theory and given immediately following high working memory load (a warm functional context) will produce greater improvements in working memory performance. As an exploratory component, a subset of these experiments will be repeated in a sample of young adults with ADHD and documented executive dysfunction. As working memory dysfunction is a common and debilitating feature of many neuropsychiatric illnesses, these data will provide evidence of the potential clinical impact of next-generation personalized neuromodulatory therapies.

Primary outcome variable(s)
Brain network responses to single pulse TMS to prefrontal area with high regional controllability versus low regional controllability. Working memory performance pre- versus post-rTMS to a TMS target with high regional controllability versus a TMS target with low regional controllability.

Secondary outcome variable(s)
Brain network response to single pulse TMS in the context of high working memory load versus low working memory load. Working memory performance in patients with ADHD after rTMS to a high regional controllability point.

Background
For additional background information and source documentation, please refer to attachment (TDD_R01_Submitted_4IRB). Transcranial magnetic stimulation (TMS) has evolved to become one of the most widely used approaches for non-invasive neuromodulation. It is an FDA-approved therapy for treatment-resistant depression and significant data suggests that it may improve working memory

performance in both clinical and non-clinical samples (O'Reardon et al., 2007; Brunoni & Vanderhasselt, 2014). The majority of neuroscientific studies seeking to understand brain responses to TMS ignore that the brain can be in many different states when stimulation is delivered; however, brain state is naturally modulated by the functional context of experiments based on their cognitive demands. Recent efforts measuring and controlling context have underscored the impact of functional context on TMS-induced changes in behavior (Bassett et al., 2011; Calhoun, Miller, Pearlson, & Adal, 2014). Notably, previous work from our group and others has shown that visualizing a motor response potentiates evoked responses to TMS stimulation to the motor cortex (Oathes, Bruce, & Nitschke, 2008; Sparing et al., 2002). As such, we infer that applying TMS at a particular moment during a cognitive task may allow us to manipulate the interaction between brain state and the effects of TMS on brain networks. Specifically, we hypothesize that stimulation within a specific functional context will enhance network responses to TMS as well as its impact on behavior, in particular working memory. In addition to manipulating specific functional contexts of stimulation to enhance the impact of TMS on behavior, we also aim to explore the effect of specific stimulation sites on brain responses to TMS. Decades of cognitive neuroscience research have established a well-defined network of brain regions that are essential for WM and executive processes, including regions within the fronto-parietal network (FPN), such as the dorsolateral prefrontal cortex (DLPFC) and the superior parietal cortex (Wager & Smith, 2003; Rottschy et al., 2012; Owen, McMillan, Laird, & Bullmore, 2005). Furthermore, recent work from our group has demonstrated that accurate WM performance also depends on deactivation of regions within the default mode network (DMN) including the ventromedial prefrontal cortex and the posterior cingulate, and reduced functional connectivity between the FPN and the DMN (Satterthwaite et al., 2013). As in previous work, we call this constellation of activity and connectivity functional network segregation (Satterthwaite et al., 2013; Baum et al., 2017). Critically, earlier work by PI Oathes using TMS/fMRI has established that TMS can induce this same pattern of FPN activation and DMN deactivation (Chen et al., 2013). Thus, there is evidence of concordance between the brain circuits required for WM function and the brain circuits influenced using our TMS protocols. We hypothesize that stimulation during a WM task that instantiates this functional context will enhance both brain and behavioral responses to TMS. While our preliminary data guides our focus on WM, we anticipate that the interaction between functional context and stimulation may be a general mechanism of TMS response that could be extended to other brain networks and cognitive systems in future. Moreover, this study explores how we may be able to maximize the downstream brain network effects of TMS based on specific stimulation site. Specifically, we look at applying the network control theory to individualized TMS targeting. The network control theory (NCT) suggests that alterations in the activation of a single node in a brain network can lead to distributed and system-wide effects whose exact pattern depends on the structure of the network interconnecting all nodes (Liu, Slotine, & Barabasi, 2011; Muldoon et al., 2016). Originally developed in the field of systems engineering, NCT provides a framework for understanding how key nodes, or control points, can exert disproportionate influence over system function (Liu et al., 2011). NCT is applicable in systems that are controlled through signals that originate at the control point and move through the network. This description is identical to the rationale for administering repetitive TMS to a specific brain area and expecting widespread effects on brain and behavior. Despite such widespread use in disparate fields and evident similarity to our understanding of how TMS influences human behavior, there has not yet been research exploring TMS in the context of network control theory (NCT). Efforts to test such a theory are critical, as validation could provide a generalizable mechanism of TMS that would prove essential for choosing the target of stimulation, titrating stimulation dose, and personalizing stimulation to the subjects intrinsic brain network architecture. In a sample of healthy adults we will use ultra-high resolution diffusion imaging (DSI) to map the structural connectome and identify brain regions with high and low regional controllability. We will directly test whether TMS targeted to control points using NCT on a single-subject basis results in greater network responses in single-pulse TMS/fMRI recordings. Specifically, we will vary the stimulation target in a counterbalanced order across two days of TMS/fMRI, where stimulation of a prefrontal control point (with high regional controllability) is compared with stimulation of a prefrontal region with low regional controllability. During each of these TMS/fMRI sessions, we will also evaluate the impact of functional context by stimulating under counterbalanced conditions of high or low WM load. Critically, following these initial single-pulse experiments that interrogate network activation and interaction, each participant will receive rTMS in the scanner to modulate the system. We expect that rTMS targeted with NCT and given immediately following high WM load (a warm functional context) will produce greater improvements in WM performance. Furthermore, we predict that these behavioral changes will be mediated by functional network segregation. Importantly, a subset of these experiments will be repeated in a sample of young adults with ADHD and documented executive dysfunction. As WM dysfunction is a common and

debilitating feature of many neuropsychiatric illnesses (including ADHD, psychosis, and mood disorders), these data will provide evidence of the potential clinical impact of next-generation personalized neuromodulatory therapies (Shanmugan et al.,2016).

Study Design

Phase*
Not applicable

Design
We will use a 2x2x2 factorial design to probe the impact of network control theory guided targeting and functional context using single pulse TMS/fMRI. Within-session changes in working memory performance and network responses following neuromodulation with rTMS will be evaluated in healthy adults and in patients with ADHD. Healthy young adults will undergo four neuroimaging sessions. Following medical, clinical, and cognitive assessment, neuroimaging session one will consist of ultra-high resolution diffusion spectrum imaging to map the structural connectome and identify control points. This initial session will be followed by two TMS/fMRI sessions which combine experiments that interrogate circuits with single-pulse TMS/fMRI as well as rTMS to modulate circuits. The two TMS/fMRI sessions will compare brain responses to stimulation targeted on the basis of high versus low regional controllability. Target location will alternate across neuroimaging sessions two and three in a counterbalanced fashion to test our hypotheses. For each of these two TMS/fMRI sessions, stimulation will occur within a counterbalanced functional context of high versus low working memory load. Within each TMS/fMRI session, initial interrogation using single-pulse stimulation will be followed by neuromodulatory rTMS. Single-pulse stimulation that was conducted pre-TMS will be repeated after neuromodulation, in order to evaluate the effect of network control theory targeting and the functional context of recent working memory load (warm rTMS) on working memory performance and network segregation. We will also study 35 patients with ADHD and working memory deficits. In two scanning sessions, we will first identify control points and then record responses to network control theory-guided rTMS administered during a functional context of high working memory load. Subjects can also complete an optional task while they undergo an fMRI scan if the task is available.

Study duration
Each healthy control subject will spend a total of approximately 7-12.5 hours of participation in the study over 4 or 5 experimental sessions. Each participant with ADHD will spend a total of approximately 5.5-10.5 hours of participation in the study over 3 or 4 experimental sessions. Visit 1: Consent, screening, clinical interview and TMS demo (1-3 hrs) Visit 2: Baseline MRI Scan: DSI, rest, T1 and assessments (2-4 hrs) Assessments from Visit 1 and Visit 2 may be split onto multiple days in order to accommodate scheduling constraints. Visit 3: TMS/fMRI scan (1.5-2 hrs) Visit 4(-only healthy control subjects): TMS/fMRI scan 2 (1.5-2 hrs) Visit 5(or 4 for ADHD patients) (OPTIONAL): Task fMRI scan (2 hrs)

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 Center Director, who is an M.D. Facilities will include various 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 with a 64-channel head/neck array, 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
This study will recruit 50 medically healthy young adults between the ages of 18 and 28 as well as 45 patients with ADHD matched on age, sex, and race. A diagnosis of ADHD will be determined by the Young Adult Psychiatric Assessment (YAPA) or GOASSESS. We plan to enroll 95 participants in order to collect usable data from 40 healthy control participants and 35 patients with ADHD.

Subjects enrolled by Penn Researchers
95

Subjects enrolled by Collaborating Researchers
0

Accrual
Participants will be recruited from several sources. As detailed below, we have identified primary and secondary recruitment sources for both the healthy participants and ADHD patients. 1) Center for Neuromodulation in Depression and Stress (CNDS). The CNDS maintains a large pool of healthy volunteers who have indicated their interest in participating in studies of neuromodulation. Healthy participants will primarily be drawn from this source. Additional subjects, including those with symptoms of ADHD, 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 through Penn supported REDCap. The link for completion of online screening forms may be presented throughout all advertising mediums. All subjects fitting inclusion criteria will be contacted by study staff with further information about the study. Follow-up may involve an additional pre-screening form for those subjects endorsing threshold criteria for 2 out of 3 questions about ADHD on the general screener. ADHD subjects will need to pass this pre-screener in order to be enrolled, as determined by a staff member according to GOASSESS criteria. 2) The Philadelphia Neurodevelopmental Cohort (PNC) (#810336).The PNC is a large-scale study of neurodevelopment conducted at Penn. PI Satterthwaite has led the neuroimaging efforts associated with this study, which included imaging n=1,601 participants ages 8-22. The PNC will provide the primary recruitment source for ADHD participants in this study, and a secondary source for healthy participants. 3) Subjects may also be drawn from a large pool of subjects who have agreed to be contacted for research as part of our Neuropsychiatry Programs center-wide protocol (#813943). This protocol provides the Neuropsychiatry Program with common procedures including recruitment, screening, and clinical assessment. Please refer to protocol #813943 for a complete description of all subject accrual procedures. 4) Adult ADHD clinic. The adult ADHD clinic at the outpatient psychiatry practices of the Department of Psychiatry will serve as a secondary recruitment source for ADHD patients. This will complement the participants provided by the PNC, and also provide a source of participants with more severe symptoms than the community-based sample provided by the PNC. We will provide clinicians with recruitment cards and brochures, whereby they can give study details and contact information to interested patients. There will also be information about the study on the clinic website. 5) Both healthy control volunteers and patients with ADHD will also be recruited through community advertising including flyers and online postings (Craigslist, iConnect, CNDS website, Experiments@Penn, University of Pennsylvania School of Arts & Sciences UPenn Experiments). This sample should provide us with adequate data to compare the patient group to non-disordered group and compare across conditions within groups.

Key inclusion criteria
1. 18-28 years old at enrollment 2. Healthy participants: no current or past DSM-V Axis I or II diagnoses (besides past substance use disorders) 3. Healthy participants: no current use of psychoactive medication 4. ADHD participants: meets DSM-V criteria for ADHD according to the YAPA interview or GOASSESS 5. Right handed 6. For participants reporting daily use of more than 400mg caffeine/ day: willing to lower down to this level at least 1 week prior to screening visit and maintain throughout study visits 7. ADHD participants abstaining from psychostimulants: willing to not increase levels of caffeine use throughout study participation

Key exclusion criteria
1. Metallic implants, claustrophobia, or other contraindications to MRI/TMS (e.g. foreign metallic implants, pacemaker, shrapnel or other metal in/on the body that cannot be removed, claustrophobia, etc.). 2. Presence or history of medical or neurological disorders that may affect brain function.

Examples include history of significant cardiac disease, endocrine disorders, renal disease, pulmonary disease, seizures, head trauma, CNS tumors, or visual impairment (e.g., blindness, glaucoma). 3. History of psychosis (schizophrenia, schizoaffective disorder) or bipolar disorder. 4. Significant handicaps (e.g. intellectual disability) that would interfere with testing procedures 5. Recent substance use presenting the possibility of acute intoxication or withdrawal. 6. Pregnancy. 7. Not proficient in English. 8. Any other factor that in the investigators judgment may affect patient safety or compliance (e.g. distance greater than 100 miles from procedure site) 9. Any reason that impairs ability to give informed consent 10. Healthy participants: psychoactive medication use. 11. Healthy participants: first degree relative with psychosis. 12. ADHD participants: inability to refrain from stimulant medication within 24 hours of study sessions. 13. Active suicidality or current suicidal risk as determined by the investigator. 14. Opiate medication, antihypertensive medication, or any medication that interferes with fMRI recordings as per PI discretion 15. Unable to tolerate TMS 16. ADHD participants: Newly initiated psychotherapy as determined by investigator.

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.

Subject recruitment
1) Center for Neuromodulation in Depression and Stress (CNDS). The CNDS maintains a large pool of healthy volunteers who have indicated their interest in participating in studies of neuromodulation. Healthy participants will primarily be drawn from this source. Additional subjects, including those with symptoms of ADHD, 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 through Penn supported REDCap. The link for completion of online screening forms may be presented throughout all advertising mediums. All subjects fitting inclusion criteria will be contacted by study staff with further information about the study. Follow-up may involve an additional pre-screening form for those subjects endorsing threshold criteria for 2 out of 3 questions about ADHD on the general screener. ADHD subjects will need to pass this pre-screener in order to be enrolled, as determined by a staff member according to GOASSESS criteria. 2) The Philadelphia Neurodevelopmental Cohort (PNC)(#810336). The PNC is a large-scale study of neurodevelopment conducted at Penn. PI Satterthwaite has led the neuroimaging efforts associated with this study, which included imaging n=1,601 participants ages 8-22. The PNC will provide the primary recruitment source for ADHD participants in this study, and a secondary source for healthy participants. 3) Subjects will also be drawn from the Neuropsychiatry Programs center-wide protocol (#813943). In addition, subjects will be recruited from other protocols, including protocols #810336, #816281, #815814, #818621, #816275. Subjects who participated in these protocols indicated their willingness (or lack of) to be re-contacted for further research. We will preferentially recruit from subjects who have received detailed follow-up clinical phenotyping and baseline neuroimaging as part of those protocols 4) Adult ADHD clinic. The adult ADHD clinic at the outpatient psychiatry practices of the Department of Psychiatry will serve as a secondary recruitment source for ADHD patients. This will complement the participants provided by the PNC, and also provide a source of participants with more severe symptoms than the community-based sample

provided by the PNC. We will provide clinicians with recruitment cards and brochures, whereby they can give study details and contact information to interested patients. There will also be information about the study on the clinic website. 5) Both healthy control volunteers and patients with ADHD will also be recruited through community advertising including flyers and online postings (Craigslist, iConnect, CNDS website, Experiments@Penn, University of Pennsylvania School of Arts & Sciences UPenn Experiments). All recruitment materials, including but not limited to flyers, brochures, referral letters and online postings will be IRB-approved before distribution of any of these materials.

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.*
Both healthy control volunteers and patients with ADHD will be recruited through community advertising including flyers and online postings (Craigslist, iConnect, CNDS website, Experiments@Penn, University of Pennsylvania School of Arts & Sciences UPenn Experiments). All recruitment materials, including but not limited to flyers, brochures, referral letters and online postings will be IRB-approved before distribution of any of these material.

The following documents are currently attached to this item:

There are no documents attached for this item.

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

Subjects will receive compensations for completing the following procedures. Visit 1: Clinical Interview (=$40) and Test TMS Pulses (=$10) Visit 2: Baseline MRI Scan ($60) and assessments ($80) Visit 3: TMS/ MRI Scan $150 Visit 4 (for controls only): TMS/MRI Scan 2 $150 If participants have already completed some of the study procedures as a part of another study at the Center for Neuromodulation in Depression and Stress or through Neurodevelopment & Psychosis Section they will not have to complete these study procedures again and therefore will only be compensated based on new study procedures completed under this protocol. If they have already completed the clinical interview and assessments through a previous study, they may be able to complete Visit 2 assessments during Visit 1 and will be compensated $40 for Visit 1 and $60 for Visit 2. Unless the participant requests compensation after each study visit, subjects will be compensated at the end of their study participation. Subjects may receive an additional $100 if the task for Visit 5 (or 4 for ADHD subjects): Task MRI Scan is available while they are enrolled in the study and they would like to complete it. In other words, if the task is not available by time the complete Visit 4 (or Visit 3 for ADHD subjects), their study participation will be considered complete and they will not receive the additional $100. Subjects will be compensated through University of Pennsylvania supported Greenphire ClinCard. This is a reloadable 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.

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)?
No

Procedures
Potential subjects showing an interest in participation for the study will be asked to answer questions on the CNDS general screener through Penn supported REDCap, if they have not already done so. A lead coordinator will review the results of this screener and refer them to this study if they meet basic eligibility criteria. For potential ADHD participants, this means meeting threshold for 2 out of 3 questions asked about ADHD on the screening form. If they meet this threshold, they will be contacted and given a brief explanation of study procedures and time commitment involved in participation, and screened to exclude any individuals meeting clear-cut exclusion criteria. For ADHD participants, this involves filling out an additional online REDCap pre-screening form sent by a study coordinator. The questions and results of this pre-screener are determined by GOASSESS standards, and a staff member will mark the form pass or fail. The brief phone or online screen will last approximately 15 minutes. If basic eligibility criteria are met, and the pre-screener is passed, participants will be contacted to schedule their first visit. Visit #1- Consent and Screening Visit: This visit will involve both remote and in-person procedures. First, participants will be contacted to schedule a remote visit in which a coordinator will discuss the Informed Consent Form (ICF). After going through the ICF, participants will be asked to electronically sign the end of the ICF and complete a Remote ICF Attestation Form. After the ICF process, participants will be asked to complete multiple questionaries regarding their medical history, demographics, social security (for compensation), and eligibility to receive MRI scans and TMS. After the questionnaires, participants will undergo a clinical interview. If participants meet eligibility for these initial procedures, we will schedule an in-person meeting to test TMS tolerability. 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. Tolerability screening will be assessed by giving test pulses of TMS that utilize 120% of each participants estimated motor threshold level. The information collected in this initial visit will determine if the subject meets all inclusion criteria. Visit #2- Baseline MRI: During this visit, eligible participants will complete a 1 hour scan that will include ultra-high-resolution diffusion MRI and structural imaging. This first session scan will allow for mapping the structural connectome, and used to identify regions of high and low controllability. These will serve as stimulation targets for the subsequent TMS/fMRI scan sessions. This visit will also involve multiple questionnaires and assessments, including neurocognitive testing. Assessments from Visit 1 and Visit 2 may be split onto multiple days in order to accommodate scheduling constraints. Participants who have previously and recently completed the screening assessment and neurocognitive battery through he Neurodevelopment & Psychosis Section will not need to complete these procedures and their data from those assessments will be shared for the current protocol only if they consent to the current study. Visit #3-TMS/fMRI: Before TMS scans, a swim cap on each participant is marked overlying targeted brain regions as determined by neuronavigation (Brainsight). Motor threshold will be determined at the scanner just before the TMS/fMRI recordings to use in determining the 110% and 120% MT levels for TMS. Participants will have a 1-hour TMS/fMRI session including approximately 4 minutes total of repetitive stimulation as well as 2 rounds of single pulse TMS in scans each about 12 minutes. Target location (site of high controllability versus site of low regional controllability) will alternate across TMS/fMRI sessions and in a counterbalanced fashion. During this scan, participants will also perform a working

memory N-back task several times. rTMS protocol: We will use the intermittent theta burst stimulation pattern (iTBS) of rTMS (Huang et al., 2005) at 110% resting motor threshold for each site for each participant. The iTBS will be administered using standard protocol pulse parameters: 2s of stimulations (30 stimulations) followed by 8s gaps and repeated 20 times for 600 stimulations total. fMRI recordings will be collected for 5 minutes before iTBS starts and also during each 8s gap so that cumulative dose as neuroplasticity is induced can be recorded. We have successfully employed 1, 5, and 20 Hz protocols as well as theta- burst rTMS using our in scanner rig without significant heating of the coil elements. This is mainly due to the air cooling system that we developed and that is now an optional equipment purchase from Magventure for their MRI compatible TMS system. Visit #4- TMS/fMRI 2 (for non-symptomatic subjects only): This visit will be identical to visit #3, but the site of stimulation will be the opposite site from the first TMS/fMRI session. Target location (site of high controllability versus site of low regional controllability) will alternate across TMS/fMRI sessions and in a counterbalanced fashion. We will use the motor threshold determined at the first TMS/fMRI session for Visit #4. Participant Monitoring During MRI/ TMS Procedure: For maximal safety we will have a medically trained individual (Dr. Sattherthwaite, TDB MD project staff or similarly trained nurse/physician) with advanced life support and TMS training on call at every study visit that includes rTMS with any participant (patient or healthy) to respond to any potential medical situations arising from doing TMS/fMRI. Study staff will be trained by the study PIs (Oathes and Satterthwaite) to recognize the most common medical conditions arising from rTMS administration (syncope and seizure) and how to effectively report these outcomes as well as minimize discomfort for participants in the unlikely event that these events occur. Only individuals trained by the PIs will dispense TMS. The medical team member will also be available for consultation during these sessions for less medically urgent issues that participants may inquire about (e.g. common temporary headaches or discomfort from TMS). As part of our medical campus and for all scans, emergency personnel and equipment are immediately available to the MRI room should the need arise. In addition, an experienced technician and a member of the study team will administer TMS during the MR session and will ensure participant safety and well-being. If the participant complains of feeling claustrophobic or excessive discomfort from TMS and does not wish to complete the MRI, the study will be terminated. Visit #5 (or #4 for ADD/ADHD patients)(OPTIONAL)- Task fMRI scan (for all subjects): This visit will only take place if the task is available, and the participant wants to complete it. This visit will take place over a 1-hour fMRI session. Participants will complete several fMRI scans while completing tasks relevant to attention and learning.

The following documents are currently attached to this item:

There are no documents attached for this item.

Deception
Does your project use deception?
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 working memory load (high vs low) by stimulation site (high vs low controllability) ANOVA will be done both on working memory performance (d prime sensitivity) as well as fMRI voxelwise brain responses. In addition, the group level factor (ADHD or Healthy) will be added to the same model for a separate mixed-effects ANOVA.

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
Patients entering the study will be given a unique identifying code. This code will be used on all data obtained from scans or the medical record. Only one password protected document connecting the code with the participant name will exist. Everything will be immediately coded and this coded information will be stored in secure cabinets inside locked rooms or in password protected, IRB compliant online databases, such as REDCap.

Sensitive Research Information*
Does this research involve collection of sensitive information about the subjects that should be excluded from the electronic medical record?
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 if they prefer phone (and cell or home) or email. 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.

Data Disclosure
Will the data be disclosed to anyone who is not listed under Personnel?
Deidentified information may be shared with collaborating researchers within the University of Pennsylvania and at collaborating institutions (CHOP). Subjects who choose to participate in other projects at the Center for Neuromodulation in Depression and Stress will provide written permission (within ICF) to have their data shared between studies so that they do not need to repeat duplicate study procedures. There will be no additional documentation for this study that identifies these subjects as partaking in other studies.

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 one of 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 subject 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. Subjects will automatically receive an electronic copy of the ICF. 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 participant meets initial eligibility, they will be invited to an in-person meeting where we can provide a paper copy of the ICF upon request.

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*
No

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
Clinical assessment: In the screening, we plan to ask if potential participants have had any diagnosis or treatment for a psychiatric or neurological condition. Some participants may experience emotional discomfort when answering some of the questions or talking about their personal feelings or life events. Participants may choose not to answer any question. MRI Scan: There are no known risks associated with MRI scans for neurologically healthy subjects except that participants may experience discomfort as they will be required to lie still in a confined area. Participants 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 even with ear plugs worn by all MRI study participants. If a subject has a problem with feeling uncomfortable while inside the scanner, they may stop this study. 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. 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 so we will exclude any participants TMS: Based on the latest safety guidelines for using TMS by a panel of experts in Neurology, Epilepsy, Psychology, Bioethics, Magnetic Resonance, Neuroscience, Hearing Disorders, and related disciplines (The Safety of TMS Consensus Group), a list of risk factors and guidelines for using TMS has been published (Rossi et al., 2004, 2009, 2021). The list recognizes TMS used in clinical as well as research applications, including TMS in an MRI environment. The most common side of effect of TMS is a mild headache, which approximately 25% of patients experience. We demonstrate TMS at the initial screening visit to ensure participants are comfortable receiving TMS. Headache intensity following administration of TMS could vary in severity from mild to intense. The effects of a more intense headache could last into the next day. Although uncommon, some subjects have experienced nausea, lightheadedness, and dizziness during the experiment. Seizure risk is the biggest safety concern in TMS research. For single-pulse TMS, this risk is listed as Rare. For high frequency rTMS (proposed here), the risk for seizure induction is listed as Possible but less than 1% in normals (healthy participants). With proper screening (outline above), and administering TMS to well over 100 participants, we have never induced a seizure. Consistent with these guidelines that list the risk of even transient cognitive or neurophsychological problems as overall negligible, most studies suggest a benefit for cognitive performance with similar protocols and we expect a similar outcome (transient, up to 15 min) for our experimental task. Risk of Breach of Confidentiality: Breaches in confidentiality could impact future insurability and/or employability if, for example, low cognitive performance is detected or a psychiatric/neurological condition is documented. 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.

Potential Study Benefits
There is no promise of benefit to subjects in this study. There is no benefit to receiving the MRI scans or to the testing. The scans and testing are performed only for research and the results are not routinely shared with participants. However, in the event that MRI abnormalities are discovered, subjects will be informed of the finding. Participants experience the indirect benefit of contributing to scientific knowledge.

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

Data and Safety Monitoring
1. Before any investigator or assistant is allowed to enter the scanner room, they are required to take an extensive MRI safety course (with annual refresher courses) that deal with powering down (or quenching) the magnet for patient safety and with established procedures for expediting participant contact with emergency medical personnel, should the need arise. These courses are run by CAMRIS as

a prerequisite for obtaining privileges to book and use scanner time. 2. Participants will already be lying down on the scanner bed during scans. In the event of a seizure, participants will be taken out of the magnet bore immediately and the barriers on both sides of the detachable bed will be raised to prevent injuries from falls. This event will qualify as a medical emergency and procedures outlined below will be followed: 3. Emergency responding in the scanner is facilitated by having two research staff running a scan. In the event of an emergency, one of these individuals remains with the participant and undocks the scanner bed from the magnet bore. This bed can easily be wheeled out of the scan room to facilitate speedy access to arriving emergency medical personnel. The second researcher calls 9-1-1 from the scanner suite and gives details of the participant's level of medical distress and location. This person next calls the Faculty Administrator for CAMRIS, Mark Elliot, Ph.D., to notify him of the event and to make use of his expertise in scanner emergencies. Next, this person goes out to the front of the scanner building to flag down arriving emergency personnel and to direct them to the participant. 4. Dr. Theodore Satterthwaite MD, is a licensed physician and will be on call during all scans (or another medically trained individual) to respond to any more subtle potential medical situations arising from doing TMS/fMRI. Drs. Satterthwaite and Oathes will be involved in training research personnel in proper use of TMS/fMRI equipment and in detecting the onset of seizures. 5. These guidelines are in full agreement with CAMRIS safety protocols and with published guidelines by a panel of experts in conducting TMS/rTMS and TMS/neuroimaging work for both research and clinical purposes (Rossi et al., 2009). MRI compatible TMS equipment is used in a novel experimental context but well within recommendations by the equipment manufacturer who continues to work closely with the CNDS and the applicant.

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit Assessment

There is essentially zero risk of harm from the research procedures (MRI,TMS, computerized tasks). The potential benefit to society through the increased understanding of the effects of TMS on cognition 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. In this study we will be using single pulses of TMS and short rounds of high frequency rTMS. For single pulse TMS, the risk is considered as rare. For high frequency the risk for seizure induction is listed as possible but less than 1% in healthy participants (Rossi et al. 2021) There is no evidence of increased risk for using single pulse and rTMS on unmedicated patients with ADHD.