TMS modulation of insula-related brain networks (TMS_INS)

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PURPOSE OF THE STUDY

The purpose of this study is to investigate the modulatory effects of repetitive transcranial magnetic stimulation (rTMS) on functional connectivity with the insula. Functional connectivity (FC) measures the interaction between brain regions, and recent neuroimaging studies have used FC to investigate how addiction affects FC among pertinent brain regions. rTMS, which can excite cortical neurons, has shown promise as a method to manipulate brain connectivity and could be used therapeutically to treat addiction. However, we first need more information on brain FC and how it relates to behavior, in order to guide rTMS target selection.

Insula FC is highly relevant to tobacco addiction. In a recent paper, we reported on pre-existing differences with insula FC among smokers who underwent a subsequent quit attempt. We found greater insula FC with the sensorimotor cortex and putamen among smokers who remained abstinent, compared to those that relapsed [1]. We need to conduct this 'proof of principle' study, to determine whether rTMS can acutely strengthen insula - sensorimotor FC in healthy controls.

Aim 1: To investigate the effects of excitatory rTMS on the insula-sensorimotor FC
Hypothesis IV: rTMS will increase the strength of insula-sensorimotor FC
Hypothesis V: The degree rTMS increases FC will be positively correlated with increased distress tolerance.

DESIGN & PROCEDURES

Overview: This study has a within-subject design. Healthy controls will be recruited from the community, consented, screened for eligibility, then scheduled for 2 MRI scans and 5 rTMS sessions.

We will advertise on local radio, television stations, internet, flyers, and in the newspapers for volunteers for the study. We will also recruit volunteers from the Brain Imaging and Analysis Center (BIAC) subject pool (Pro00010672). Participants who qualify over the phone or via an internet-based survey and are interested in participating will be scheduled for further screening at the study site. The informed consent and screening session will last about 1 to 1.5 hr. All aspects of the study will be described and informed consent will be obtained by the PI, study coordinator, or data technician. Breath and urine samples will be collected in order to screen for drug use and recent alcohol use. Women of child-bearing potential will undergo urine pregnancy testing. Detailed inclusion/exclusion criteria are described below in the Selection of Participants section.

Each subject will also complete a Duke-UNC Brain Imaging and Analysis Center (BIAC) approved fMRI subject screening form and a TMS Adult Safety Screen (TASS) form. A medical history questionnaire will be completed, and it will be reviewed by the study physician if necessary. Participants who meet all selection criteria will subsequently be scheduled for their study days.

On the first study day, participants will undergo a 1-hour MRI session. This visit will last approximately 2 hours.

On the 2nd through 6th study days, participants will undergo a 1-hour rTMS session each day. On the 7th study day, participants will undergo a 1-hour MRI session– this session is identical to the first MRI study day. All study days will be completed within 3 weeks. See Table 1 below:

Table 1: List of Study Visits and Activities

Study Day	Activity
0	Consent and Screening
1	MRI session
2	Active rTMS
3	Active rTMS
4	Active rTMS
5	Active rTMS
6	Active rTMS
7	MRI session

Magnetic Resonance Imaging (MRI):

During the MRI scan, participants will be administered a resting-state functional connectivity run, a scanner version of the PASAT (see below), a diffusion tensor imaging scan, and a structural anatomical scan. Participants will be in the MRI scanner for 1 hour.

TMS Study Interventions: TMS procedures will occur in the Noninvasive Neuromodulatory Neuroscience Lab in the Department of Psychiatry and Behavioral Sciences, Duke Clinic South and in the BIAC facilities. Initially, a motor threshold (MT) will be determined by placing a figure 8 TMS coil on the subject's scalp and applying individual TMS pulses to left motor cortex. MT is defined as the minimum magnetic flux needed to reliably elicit a threshold EMG response in a target muscle. MT is the standard in the field for determining the dosing intensity of TMS for each individual and to reduce seizure risk. The motor evoked potentials (MEP) for the contralateral first dorsal interosseus (FDI) will be measured with EMG. The scalp region producing the largest amplitude MEP will be identified. At that scalp location, the lowest TMS intensity able to elicit 5 MEP's of ≥50μV in peak-to-peak amplitude in 10 trials at this site will be determined using a descending method of limits procedure. Individual MT will be used to determine the intensity of stimulation for each individual, as recommended by safety guidelines.

TMS application during TMS sessions: The subject will be seated comfortably in a chair. Earplugs will be worn to protect hearing. TMS coil placement will be guided by a neuronavigational system (Brainsight: Rogue,Instruments Montreal, Canada) using infrared technology to co-register head and coil locations with subject MRI recordings with millimeter accuracy. The coil will be placed using Brainsight over the sensorimotor cortex targeted to a location chosen based on the subject's baseline functional connectivity found in the initial imaging session. TMS intensity will be 100% motor threshold. 10 Hz rTMS will be applied for 5 s, followed by a 20 s inter-train interval. This will be repeated for 16 minutes, resulting in a total of 2000 pulses. During the 20 s inter-train interval, the subject will perform the easy phase of the PASAT task. A rTMS side effect rating scale will be administered after each rTMS session. The 5 TMS sessions will each last about an hour.

SELECTION OF PARTICIPANTS

Subject identification and recruitment: Prospective participants, ages 18 – 55, will be recruited for the study through local radio, television stations, internet, flyers, newspapers, the BIAC subject database, and by word-of-mouth. Potential participants will call our office or fill out an online questionnaire and they will be given a brief description of our studies and will be asked questions to determine interest and eligibility.

Assessment of eligibility: Each potential subject will be contacted by telephone and the study will be described. We will ask the potential subject for information including name, telephone

number, address, age, smoking history, and a brief medical history. Participants who qualify and who are interested in participating will be scheduled for the screening.

Inclusion criteria for all participants:
1) generally healthy
2) between the ages of 18-55
3) right-handed

Exclusion criteria for all participants:
1) significant health problems (e.g., current and uncontrolled liver, lung, or heart problems) or presence of medical illness likely to alter brain morphology (including history of seizure, history of epilepsy in self or first degree relatives, stroke, brain surgery, head injury, and known structural brain lesion)
2) current diagnosis of Axis I psychiatric disorders (e.g., depression, anxiety disorder, schizophrenia)
3) meet DSM-5 criteria for current substance use disorder other than nicotine
4) use of psychoactive medications that would result in a positive urine drug screen
5) Current use of medications known to lower the seizure threshold
6) positive breath alcohol concentration
7) presence of conditions that would make MRI unsafe (e.g., metal implants, pacemakers)
8) among women, a positive urine pregnancy test
9) vision that cannot be corrected to 20/40

Compensation*:* Participants will receive $280 for completing the entire study. In addition, participants can earn up to $10 on each MRI study day based on their performance for a maximum total compensation of $300. Participants that decide to withdraw from the study before completion will be compensated $20/hour of participation on a pro-rated basis for the part(s) of the study that they have completed.

Subject competency: Only competent participants will be allowed to participate in the study.

RISK/BENEFIT ASSESSMENT

Magnetic resonance imaging (MRI): There are no known long-term health risks to the use of magnetic resonance imaging per se when operated within FDA guidelines. However there are safety concerns posed by the strong magnetic fields used to make images. All scans conducted under this protocol meet the FDA's guidelines for non-significant risk for static field strength, specific absorption rate (SAR), time varying magnetic fields (dB/dt), and acoustic noise.

MRI provides clinically relevant anatomic and functional information non-invasively and with minimal risk, if the well-known contraindications (such as pacemakers) and potential hazards (such as attraction of metallic objects) are avoided. There have been no ill effects reported from exposure to the magnetism or radio waves used in this test. However, it is possible that harmful effects could be recognized in the future. A known risk is that the magnet could attract certain kinds of metal. Therefore, we will carefully ask participants about metal within their bodies (this includes certain dyes found in tattoos).

Incidental MRI Findings: It is possible that this study will identify information about a subject that was previously unknown. Such incidental findings, if any, will not be shared with the subject unless the incidental finding is determined to be likely to cause premature death if untreated. Should such life-threatening results be uncovered through the MRI scan the information will be shared with the principal investigator of the study who will share the information with the subject.

Women of childbearing potential: Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Women will be screened with a urine pregnancy test before the MRI scan. Positive pregnancy tests are exclusionary. Urine pregnancy tests will be administered and interpreted by an individual who has completed training from the Duke University Department of Obstetrics and Gynecology in accordance with the IRB policy statement regarding pregnancy testing 1/14/2013.

TMS: There are no known long-term health risks to the use of TMS per se when operated within consensus safety guidelines, which include the rTMS intensity and timing parameters considered safe, as well as training, planning for, and managing emergencies (Rossi et al., 2009). We will follow these guidelines, and have incorporated them into our screening and session procedures.

The greatest potential risk in the use of TMS is seizure. The Rossi et al. (2009) consensus safety report stated that "The occurrence of seizures has been extremely rare, with most of the few new cases receiving TMS protocols exceeding previous guidelines, often in patients under treatment with drugs which potentially lowered the seizure threshold" [2]. As Rossi et al. delineate, "rare" means that up to the end of 2008, 16 cases of seizure related to TMS had been reported, out of tens of thousands of TMS sessions over the last two decades. Seven occurred before safety parameters were established in 1997. These seizures appeared to be the result of excessive stimulator intensity, pulse frequency and train duration and too short inter-train intervals, in various combinations, and resulted in the establishment of safety guidelines for each parameter [2]. To reduce the risk of seizures, participants will be carefully screened for a history of seizures, epilepsy, or a family history of epilepsy (and their neurological status in general). Participants will also be screened for use of medications that could decrease seizure threshold (e.g., olanzipine). Personnel who administer rTMS are trained to recognize a potential seizure event and to act as "first responders" in order to administer appropriate initial care. The first-aid response consists of making sure the subject is physically safe for the duration of the seizure. This involves moving the participants out of the TMS chair and onto the floor lying down on his or her left side. The subject will be kept lying down on his or her left side, while the staff call emergency medical help, via a 911 call. Resources available in the laboratory include a first-aid kit and immediate phone access. A seizure constitutes a reportable adverse event, and will thus be immediately reported to the IRB via the Safety Events Form mechanism.

Other adverse effects of TMS include headache and hearing effects. Stimulation over superficial scalp tissue can result in headaches, typically of a muscle-tension type, and local muscle aches, especially with high-frequency TMS. Headaches usually develop during or immediately after the stimulation, may last for minutes to hours following the end of the stimulation, and usually respond promptly to single doses of over the counter pain medications. Cramped conditions extended in time within frameless stereotaxic apparatus can also lead to head and body aches. These aches are usually managed easily with over-the-counter analgesics. In addition, TMS exposure without hearing protection can result in hearing loss and tinnitus. Thus, participants will wear ear protection (ear plugs) during TMS exposure.

Costs to participants: Participants will not incur any costs associated with participating in the study. All the study costs, including any procedures related directly to the study, will be paid for by the study.

DATA ANALYSIS & STATISTICAL CONSIDERATIONS

Behavioral and self-report data will be analyzed using SPSS (Chicago, Ill), with significance set to alpha = .05. Prior to hypothesis testing, functional data will be preprocessed using FSL (Oxford, UK) to remove noise and artifacts. Images will be normalized to a template, motion-corrected, high-pass filtered, and spatially smoothed (8 mm FWHM). Functional connectivity will be analyzed using the Conn toolbox and an insula-seed region of interest, defined using PickAtlas [3]. Activations will be considered significant at $p < 0.05$ with a minimum cluster extent threshold of 5 contiguous voxels. Participants who do not follow task instructions, or those with > 3 mm of movement, will be excluded from the analyses.

DATA & SAFETY MONITORING

Data collected for this study will be gathered via paper-and-pencil methods, and computer-based methods. Data is either entered by hand into an electronic spreadsheet or automatically downloaded from a computer. All paperwork and electronic files will be checked by the research scientist for completeness on a daily basis. All PHI is stored in a locked file cabinet and only accessible by study staff. Internal audits to ensure quality assurance occur at the beginning of data collection, mid-way through and at the end of participant enrollment.

fMRI processing will be performed using custom MATLAB software, SPM and FSL. Analysis will include examination of functional connectivity. Changes in post-processing procedures may occur during the duration of this protocol but will not increase the risks associated with these experiments.

Behavioral and questionnaire data will be analyzed using SPSS using standard statistical procedures.

Adverse events (AE) and protocol deviations will be collected on a daily basis. The principal investigator will report all serious adverse events and unanticipated problems relating to the study in an expedited manner to the Duke University Health System (DUHS) Institutional Review Board (IRB) office and all applicable regulatory authorities in accordance with the Center's standard operating procedures.

PRIVACY, DATA STORAGE & CONFIDENTIALITY

Participants will be informed, in their consent forms, of the data storage and confidentiality safeguards, which are practiced according to current HIPAA regulations.

All MRI data will be stored on a secure server. All PHI is removed from the scanning data before it is posted on the secure server and is coded with a unique id.

Except when required by law, the subject will not be identified by name, social security number, address, telephone number or any other direct personal identifiers in the study records. The participant will be assigned a unique code number and the key to the code will be kept in a locked file in Dr. Addicott's office. Paper records will include only those identifiers necessary for tracking purposes (subject ID). Computer records will be stored in a database on a secure server.

References

1. Addicott MA, Sweitzer MM, Froeliger B, et al. Increased Functional Connectivity in an Insula-Based Network is Associated with Improved Smoking Cessation Outcomes. Neuropsychopharmacol (2015).
2. Rossi S, Hallett M, Rossini PM, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol (2009) 120:2008-2039.
3. Maldjian JA, Laurienti PJ, Kraft RA, et al. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage (2003) 19:1233-9.