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Abstract:
The long-term objective initiated with this study is to determine which brain areas functionally contribute to learning a motor skill. Our primary hypothesis is that premotor cortex (PMC) is necessary to learn a new motor skill. Healthy adults (age 18-85) will be recruited to participate in this study at the Emory University Rehabilitation Hospital. Participants may undergo a MRI scan to acquire a structural image of their brain to target noninvasive stimulation, using transcranial magnetic stimulation (TMS) to one of two brain areas: PMC or primary motor cortex (M1). A third group of individuals will undergo a placebo stimulation protocol. For all three groups, stimulation will be used to create a transient 'virtual lesion' during motor skill training. Temporarily disrupting the normal activity of these brain regions during training will allow us to determine which regions are causally involved in learning a new motor skill. The primary outcome measure will be the change in skill after training in each group. We anticipate the group receiving sham stimulation or stimulation to M1 will have greater increases in skill learning than the group receiving stimulation to PMC.

Introduction and Background:
Movement is necessary for animals to interact with their environment. Learning to coordinate motor sequences is essential for completing tasks necessary for daily living, such as tying a shoe or speaking. Recent findings in humans suggest that sequences are represented in premotor cortex once learned[1]. Studies in songbirds have also shown that the premotor cortical area HVC (abbreviation used as proper name) encodes sequence-specific information[2-4]. In humans, dorsal premotor cortex (PMd) is involved in the planning of execution of hand movements [5], but it is currently unknown if this premotor cortical area is also involved in the acquisition of sequences. Noninvasive brain stimulation, such as transcranial magnetic stimulation (TMS) can be used to create a 'virtual lesion,' disrupting neural activity in a specific brain region to identify whether it is causally involved in a specific behavioral process [6-8]. In this paradigm, a magnetic field passes through the skull and induces an electric current that stimulates neural tissue. This stimulation disrupts any ongoing neural processes, creating the 'virtual lesion.' This effect is temporary and does not have persistent effects when applied in the way proposed in this study. Therefore, we will use TMS to disrupt premotor cortex activity during motor learning to determine the role of human premotor cortex in sequence learning.

Aim 1: Determine the roles of premotor cortex and primary motor cortex in motor sequence learning.
Outcome Measure: Degree of sequence learning after receiving one of three types of stimulation: premotor cortex stimulation, primary motor cortex stimulation, or sham stimulation.
Aim 2: Evaluate the effect of sequence learning on motor cortical excitability.
Outcome Measure: Change in cortical excitability after sequence learning.
Exploratory Aim 3: Examine the relationship between sequence learning and cortical excitability.
Outcome Measure: Correlation between the amount of sequence learning and change in cortical excitability after learning.

Participants and Recruitment:

Based on effects reported in previous literature using a similar experimental paradigm and participant populations[9, 10], we anticipate that 30 participants per group (N=90 total) will provide sufficient power to test the primary study hypotheses. Therefore, this study will recruit 90 healthy men and women aged 18-85. Subjects will be identified and recruited through multiple approaches. Local University and community postings will be used to identify and recruit the healthy control participants. Additionally, partnerships with collaborators within the Division of Physical Therapy, Emory School of Medicine and Emory Healthcare will be utilized in subject identification and recruitment. Initial contact may be made by Dr. Borich or one of his associates.

Informed Consent. The letter of informed consent will be used as a template to describe what is being asked of the participant, the risks and benefits associated with participation etc. to the participant. The consent form will be explained by a member of the research team. At this time the individual making contact will also be available to answer any specific questions that may arise. Informed consent will be conducted by either Dr. Borich or a research coordinator in private-either in the research lab or a single-occupant office.

In testing sessions performed at the Neural Plasticity Research Laboratory (NPRL), participants will undergo: 1) noninvasive targeting of cortical locations by stereotactic neuronavigation using transcranial magnetic stimulation (TMS), 2) TMS measures of cortical excitability and neurotransmitter signaling, and 3) a motor learning paradigm. The duration of the testing session will be less than 3 hours. Participants may also be asked to complete a single magnetic resonance imaging (MRI) session prior to testing in the NPRL. Overall, participants will complete up to two study visits.

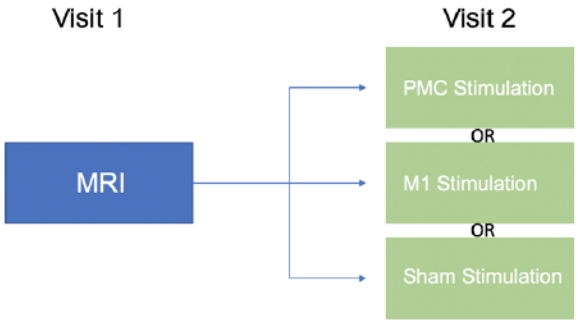

Figure 1. Experimental Design. Visit 1 will consist of a MRI session to acquire a structural image that will allow us to identify the target site of stimulation. Visit 2 will consist of a motor learning paradigm, during which one of three TMS conditions will be applied: premotor cortex (PMC) stimulation, primary motor cortex (M1) stimulation, or sham stimulation.

Inclusion Criteria. This study utilizes non-invasive brain stimulation, which is associated with minimal risk. To further minimize any risks associated with the stimulation, every subject will be informed of the potential risks of participation in the consent form and will complete a form that screens for any potential factors that could increase risk. The PI will use this information to determine eligibility. Inclusion criteria include (1) no history of movement impairment or neurodegenerative disease (2) right handedness (3) no contraindication to transcranial magnetic stimulation (TMS)[11] or magnetic resonance imaging (MRI).

Exclusion Criteria. Any participant will be excluded if they: 1) are outside the age range of 18-85, 2) have a history of head trauma or neurodegenerative disorder, or 3) report contraindications

to TMS. Participants over age 65 will be asked to complete the Montreal Cognitive Assessment, and participants with a score of 25 or lower (out of the "normal" range) will be excluded.

Experimental Design: Participants will complete up to three study visits: a MRI session and a TMS session (**Figure 1**). During the TMS session, participants will be randomly assigned to receive one of three types of stimulation during the motor learning paradigm: TMS over premotor cortex (N=20), TMS over primary motor cortex (M1, N=20), or sham TMS over premotor cortex (N=20). Groups will be gender- and age- matched. Motor performance and cortical excitability will be assessed before and after the motor learning paradigm.

MRI Acquisition

Enrolled participants may complete a MRI scan prior to the experiment to obtain a structural brain image that will be used for guided navigation during TMS protocols. T1-weighted images will be acquired at the Center for Systems Imaging at Emory University on a Siemens Prisma 3T scanner (TR = 7.4ms, TE = 3.7ms, flip angle $\theta = 6°$, 1 mm isotropic resolution, scan time=3.2min). Data will be stored on Emory University's secure network server.

TMS Procedures

Guided navigation will be used throughout the session in real-time to ensure consistent spatial localization of TMS application. BrainSight software (Rogue Research Inc.) will be used to localize stimulation over the motor representation associated with the target muscle, which will be the first dorsal interosseous (FDI) muscle of the hand. Electromyography (EMG) will be used to measure TMS-motor evoked potentials (MEPs) of the FDI muscle during all testing conditions. The resting motor threshold (RMT) will be defined for each hemisphere as the stimulus intensity required to elicit a MEP response greater than 50μV in over 50% of trials.[12] During the motor learning paradigm, sham or real TMS pulses will be delivered over premotor cortex or M1 at a stimulation intensity of 80% RMT time-locked to the presentation of specific visual stimuli (described in further detail below). Before and after the motor task, participants will receive blocks of TMS at 120% RMT and between 30 and 80% of maximum stimulator output to create an input/output curve to evaluate cortical excitability.

Motor Sequence Learning Paradigm

A modified version of the serial reaction time task (SRTT)[13] will be used to assess motor sequence learning in all study participants (**Figure 2**). During this task, the left hand will be placed on a button box so that the four fingers will press specified keys. Four colored squares will appear on the screen, and participants will be instructed to press the button that corresponds to a target square located beneath the four colored squares. The button presses will occur in a repeating pattern, and response time will be measured to indicate how well the pattern is learned. There will be blocks of random sequences at the beginning and end of the test blocks that will be used

Figure 2. Example trials of SRTT. Four boxes on the top of the screen correspond to four buttons on a button box. The target box on the bottom indicates which button to press. The colors change each trial so the participant cannot learn the sequence of colors.

to assess general task performance, and there will be five blocks in between that will be used to train the sequence. A follow-up block of the task will be performed 30 minutes following training to test short-term retention of skill.

Risks and Discomforts:
The risks are not much greater than the risks in everyday life. These procedures will be conducted according to published safety standards. The risks are as follows:

Magnetic Resonance Imaging (MRI): There is very little known risk associated with undergoing an MRI scan. MRI is used routinely in hospitals around the world. A small number of people may find lying still inside the MR scanner uncomfortable and stressful. If this occurs, the participant will be brought out of the scanner and the study will be stopped. Some people are also uncomfortable being in small places (*i.e.* claustrophobia). Because the MRI scanner is a small space, the participant may also be uncomfortable lying inside it. If the participant does feel this way, they will be brought out of the scanner and the study will be halted. The MRI also makes loud noises that the participant may find uncomfortable. They will not be able to participate in study if they have any metal or surgical implants that may be affected by the strong magnetic fields used in the MRI process or may cause tissue damage associated with dislodging the metal and/or for the objects to become heated during the scan and cause a burn. Most implants are not affected by MRI, but if the participants have any of the following, they will not be able to participate in the MRI study:

- pacemaker
- brain aneurysm clip
- ear implant (cochlear)
- recent surgery or tattoos within the past 6 weeks
- possibility of pregnancy
- electrical stimulator for nerves or bones
- implanted infusion pump

If the participant has any of the following, we will contact the MRI technologist to ensure their safety:

- history of any eye injury involving metal fragments
- they have been a metal worker (grinding, machining, or welding)
- artificial heart valve
- orthopedic hardware (artificial joint, plate, screws, rods)
- other metallic implants (prostheses)
- coil, catheter of filter in any blood vessel
- ear or eye implant
- shrapnel, bullets, or other metallic fragments
- medication releasing skin patches (nicotine, birth control, nitroglycerine)

This type of brain scan is not designed to detect problems of the brain. A radiologist will not be reading the scan. However, it is still possible that we will see something on the scan that is potentially abnormal, but may be nothing. If this happens, we will discuss it with the participant. This may cause them to seek further medical treatment and incur costs associated with that.

Motor performance tests: There are no known risks associated with these tests. They may however be difficult at times, and if the participant becomes discouraged and would like to stop, they can tell the researcher.

Electroencephalography (EEG): Collection of EEG involves application of electrodes over the scalp to measure brain activity. All electrodes do not contact the skin. A gel provides the contact between the skin and the recording electrodes. In rare instances it is possible that the skin may be sensitive to the gel or rubbing alcohol used for surface recordings. In such cases a skin rash is possible. The conductive gel is water-soluble and washes out quickly with warm water and shampoo.

Transcranial magnetic stimulation (TMS): Safety standards for the application of TMS have been developed. Trained operators will follow these standards during this study to minimize the risk. The TMS machine will always be run at a rate and a frequency that are known to be safe. There is a potential risk of causing a seizure in people with a history of seizures (e.g. epilepsy); however, there has never been a report of a seizure associated with the type of TMS used in this study (i.e. single and double pulse TMS). Participants will not be eligible to participate in this study if they have a history of seizure. There is a possible small risk of headache, scalp pain, toothache or scalp numbness associated with single and double pulse TMS. Each of these side effects is transient (i.e. does not last). The clicks associated with single and double pulse TMS are loud and could potentially damage the participant's hearing with prolonged exposures. To minimize this risk, participants will be asked to wear earplugs during the testing session.

There may be other risks that have not yet been identified, and unexpected side effects that have not been previously observed may occur.

Statistical Plan:
A skill score (SS) will be calculated as the difference between performance on the random blocks minus the average performance on the patterned sequence in the test block to determine how well the patterned is learned. Percent change in SS will be used to index sequence-specific motor learning while controlling for general improvements in motor performance. One-way ANOVA will be used to test for differences in sequence-specific skill acquisition and sequence-specific skill retention between the groups that received different types of TMS stimulation. R statistical packages will be used for statistical analyses. Secondary statistical analyses will use a repeated measures ANOVA to examine differences in cortical excitability before and after motor training. Significance level will be set at $\alpha \leq 0.05$.

Compensation:
Participants will get $20 for each completed study visit, to compensate them for their time and effort. If they do not finish the study, we will compensate them for the visits they have completed. They will get $40 total if they complete two study visits.

Data Safety and Monitoring

To ensure safety and minimize risks to study subjects, the following data safety monitoring plan (DSMP) will be implemented in accordance with the Emory University IRB DSMP guidance document:

The primary risk for subjects participating in this study is the risk of seizure associated with transcranial magnetic stimulation (TMS). Although no seizures have been reported as a direct result of the type of stimulation in this study, to minimize any risk of seizure, we will not enroll individuals with a history of seizure. A TMS screening form (adapted from [11] will be administered for each subject prior to beginning the study to identify potential factors that would place the subject at increased safety risk (e.g. epilepsy or epileptogenic medications).

During testing, TMS will be performed using stimulation parameters within established safety guidelines [11]. Subject status will be monitored continuously during testing by study staff for potential adverse events. Transient headache and scalp discomfort are the most common adverse effects reported but are not considered serious. If a subject reports either of these events during testing, we will advise participants to follow their typical routine for managing these types of symptoms and to follow up with study staff if any discomfort persists. If persisting symptoms are reported, we will recommend that the subject follow-up with their physician and we will document the event. Contact information for the PI and the Emory University IRB are provided in the consent form. Each subject will receive a copy of the consent form to facilitate reporting of any potential adverse event. In the event that an unforeseen medical emergency should occur, all testing will be conducted in the Center for Rehabilitation Medicine where there is access to emergency medical equipment and a physician present in the building. We will also dial 911 in the case of a medical emergency to provide additional emergency medical services to ensure patient safety and care.

Members of the study team will review study documentation as needed with an informal review scheduled every six months to determine if there are trends for adverse events. If trends are observed, they will be reported to the IRB and the DSMP will be revised to address the presence of these observed adverse events. There are no specific stopping rules for this study. All protocol deviations, adverse events deaths and non-compliance will be reported in accordance with Emory University IRB Reportable Events guidelines.

To assure data accuracy and integrity, only approved study procedures will be performed by members of the study team. If it becomes known that a member of the study team is not following these procedures, it will be reported to the PI and the Emory University IRB. Storing electronic data on a secured server on the Emory University network will be used to maximize confidentiality of study data. Hard copies of any forms with identifying information will be stored in a locked file cabinet in the research laboratory that is also locked when study staff are not present. The PI will perform routine data and protocol verification no less than every six months. Study staff will also comply in full with any external data-audit process.

Confidentiality

Whenever possible, a study number, rather than the participants' name, will be used on study records. The participant name and other identifying information will not appear when we present or publish the study results. Study records can be opened by court order. They also may be provided in response to a subpoena or a request for the production of documents.
Certain offices and people other than the researchers may look at study records. Government agencies and Emory employees overseeing proper study conduct may look at your study records.

These offices include the Office for Human Research Protections, the Emory Institutional Review Board, the Emory Office of Research Compliance. Emory will keep any research records we create private to the extent we are required to do so by law. A study number rather than the participants' name will be used on study records wherever possible. Their names and other facts that might identify them will not appear when we present this study or publish its results.

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