Study Protocol

Title: Premotor cortex: A new target for stroke motor rehabilitation using transcranial magnetic stimulation

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ABSTRACT

Hemiparesis is a common consequence of middle cerebral artery stroke. While rehabilitation can improve functional motor outcomes, current strategies do not enable all stroke survivors to fully recover (Go et al., 2014). There is an urgent need for more effective motor rehabilitation strategies post-stroke. Important aspects of stroke motor recovery are driven by the same neural mechanisms that support motor learning; therefore, a stronger mechanistic understanding of motor learning will support the development of more effective treatment protocols (Nudo, 2006). Repetitive transcranial magnetic stimulation (rTMS) can promote cortical plasticity to support motor learning. Our laboratory established that rTMS of the primary motor cortex (M1) during motor training enhances motor skill acquisition in healthy adults (Buetefisch et al., 2015) and stroke patients (preliminary data). However, M1 is not a salient target for rTMS when M1 activity is disrupted after stroke. Another cortical region, the premotor cortex (PMC), may be an effective alternative target for rTMS. The current study evaluates the effect of PMC rTMS on motor learning in healthy humans. We hypothesize that PMC rTMS of either hemisphere will facilitate increases in motor performance and motor learning-related reorganization in M1 after unilateral motor training. To evaluate our hypothesis, healthy humans will complete unilateral motor training while receiving either ipsilateral PMC rTMS, contralateral PMC rTMS or control rTMS 1-3. We will assess motor performance and motor learning-related plasticity of M1 before and after training. The results of this study will support the development of more effective motor rehabilitation strategies for stroke motor recovery.

INTRODUCTION/BACKGROUND

Occlusion of the middle cerebral artery is the most common cause of stroke. Because the middle cerebral artery supplies blood to the motor cortices, middle cerebral artery stroke often impacts the integrity of the motor cortex and its associated corticospinal projections. Consequently, the majority of the 6.8 million people who have suffered a stroke in the United States experience hemiparesis as a result of the infarct (Go et al., 2014). Although stroke

survivors are encouraged to participate in rehabilitation programs, less than half of all individuals post-stroke regain complete motor function (Kelly-Hayes et al., 2003). Because motor deficits, especially of the upper extremities, can dampen the quality of life, there is an urgent need to improve current rehabilitation programs to allow more stroke survivors to achieve higher functional gains (MSc et al., 2014).

The existing literature strongly suggests that important aspects of stroke motor recovery are driven by similar neural mechanisms that support motor learning (Nudo et al., 2001). Motor learning is the process by which motor performance improves in response to training and is associated with learning-related changes in structural and functional organization in the brain (Jueptner et al., 1997a; 1997b). Transcranial magnetic stimulation (TMS) may serve as a therapeutic tool to enhance motor recovery after stroke by facilitating motor learning-related plasticity. TMS induces an external electrical current by rapidly shifting a magnetic field (Hallett, 2007). When TMS is placed over the brain, the electrical current can transynaptically activate neurons located within the targeted region and promote neural plasticity when applied repetitively (Wu et al., 2000). Currently, the majority of research evaluating the effect of rTMS on motor learning primarily focus on the application of rTMS to the primary motor cortex (M1) due to the major role of M1 in the acquisition of motor memory (Muellbacher et al., 2001). However, M1 is a not a salient target for rTMS for individuals who experience significant disruption of M1 activity post-stroke. For these individuals, the premotor cortex (PMC) is an attractive, alternative site for rTMS because the premotor cortex appears to help mediate functional improvements when M1 is disrupted in animal models of stroke (Frost et al., 2003). Furthermore, learning-related changes in PMC activity and structure have been detected bilaterally (Daselaar et al., 2003; Gryga et al., 2012), suggesting that PMC activity of both hemispheres may be associated with improvement in unilateral motor performance. Therefore, rTMS over the PMC of either hemisphere (PMC rTMS) may facilitate motor learning and would allow for the unlesioned hemisphere to be targeted when activity of lesioned hemisphere is disrupted. Together PMC is a promising target for rTMS to enhance training-related motor improvements when stroke has damaged the primary motor output system.

In the current project, we will evaluate the effect of PMC rTMS on motor performance and training-related reorganization of M1. The results of this research will serve as a step toward the development of more effective strategies for stroke motor rehabilitation. While our study will

benefit stroke research, PMC rTMS cannot be developed using stroke survivors because the variability of neural reorganization following stroke (Feydy et al., 2002) would occlude our ability to understand how PMC rTMS interacts with cortical activation during motor training. Therefore, we propose to evaluate PMC rTMS in healthy human population in the current study.

OBJECTIVES

Objective: Identify the effect of rTMS over the PMC of either hemisphere on learning when applied during unilateral motor training in healthy humans.

Specific Aim #1: Identify changes in motor performance associated with PMC rTMS during motor training.

Specific Aim #2: Identify changes in M1 excitability associated with PMC rTMS during motor training. The successful acquisition of a motor memory depends upon motor learning-related neural plasticity in the motor cortices (Muellbacher et al., 2001). Our working hypothesis is that PMC TMS of either hemisphere will enhance motor learning-related reorganization of M1 contralateral to the training wrist.

PARTICIPANT SELECTION

In order to qualify for the pilot portion of the study (Study Track A), participants must:

- Have the ability to give informed, written consent
- Be aged 18-80 years old
- Be right-handed
- Have intact cognitive abilities
- No current depression
- No neurological disease
- No contradictions to TMS
- Meet all criteria tested during an inclusion experiment
    - TMS over the extensor carpi ulnaris (ECU) hotspot must be able to evoke a motor evoked potential (MEP) in the extensor carpi ulnaris (ECU) muscle
    - MEP amplitude must increase by at least 20% as the TMS intensity increases
    - The subjects must be comfortable when receiving TMS of all strengths. If subjects cannot tolerate one or more TMS strengths, they will be disqualified.

In order to qualify for the full study (Study Track B), participants must:

- Have the ability to give informed, written consent
- Be aged 55-80 years old
- Be right-handed
- Have intact cognitive abilities
- No current depression
- No neurological disease
- No contradictions to TMS
- Meet all criteria tested during an inclusion experiment
    - TMS over the extensor carpi ulnaris (ECU) hotspot must be able to evoke a motor evoked potential (MEP) in the extensor carpi ulnaris (ECU) muscle
    - MEP amplitude must increase by at least 20% as the TMS intensity increases
    - The subjects must be comfortable when receiving TMS of all strengths. If subjects cannot tolerate one or more TMS strengths, they will be disqualified.

We will determine if a participant qualifies for the study during a screening session. Before the session begins, the participant must give informed, written consent. We will use the Edinburgh handedness inventory (Oldfield, 1971) to determine if participants are right-handed. We will assess the presence of neurological disease by asking participants to self-report their medical history and undergo a short medical exam performed by our study physician. Participants will also complete the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998) and Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Participants must score higher than 75th percentile on the RBANS and score less than a 7 on the Hamilton Depression Rating Scale (HDRS) to meet our criteria for cognition and depression, respectively. Subjects who pass a TMS safety screener (Rossi et al., 2009) will participate in an inclusion experiment. During the inclusion experiment, subjects will receive single-pulse TMS over the extensor carpi ulnaris (ECU) hotspot of the primary motor cortex. We will apply TMS pulses at different strengths (30%-80% motor threshold) and record subsequent activity of the ECU muscle using electromyography (EMG).

STUDY DESIGN AND METHODS

Pilot study (Study Track A): We found older subjects fatigue faster than their younger counterparts during motor training (preliminary data). Because we will enroll older subjects in the full study, we will use a motor training protocol that includes shorter training blocks and more rest than the protocol used in a past study (Buetefisch et al., 2015). The objective of the pilot study is to confirm that the new motor training protocol will not fatigue older subjects. We will also recruit college-aged subjects to compare the effects of the new protocol on motor performance between younger and older participants. During the pilot experiment, each subject will undergo up to an hour of motor training. Depending upon the amount of rest (non-active) time provided, the entire training protocol could take up to two hours to complete. We will evaluate the effect of motor training on motor learning by collecting kinematic and neurophysiological measurements before and after training. Fatigue caused by the motor training will be indicated by a decrease in motor performance after training. If participants become fatigued from the motor training, we will increase the amount of rest time for the remaining participants.

- Kinematic measurements: Wrist acceleration, reaction time
- Neurophysiological measurements:
    - Short interval cortical inhibition (SICI) (Kujirai et al., 1993a)
    - Stimulus response curve (SRC) (Devanne et al., 1997)
    - Resting motor threshold (rMT) (Rossini et al., 1994)

Full Study (Study Track B): We will evaluate the effect of PMC rTMS on motor learning with a double blind randomized study consisting of five experiments separated by at least 72 hours. During each experiment, participants complete motor training while receiving one of five rTMS protocols. All subjects will received each rTMS protocol once. The order of the rTMS protocols will be randomized and counterbalanced prior to recruitment. We will evaluate the effect of each rTMS protocol on training-related motor learning by collecting kinematic and neurophysiological measurements before (pre) and immediately (post), 30 minutes and 60 minutes after training. Before an experiment commences, subjects will complete the Stanford Sleepiness Scale (SSS) (Hoddes et al., 1973). If participants self-report sleepiness at the beginning of a testing session (score over 3 on the Stanford Sleepiness Scale), the experiment

will be postponed. Sleep deprivation will affect the excitability of the cortex (Civardi et al., 2001) and will reduce attention to the training.

- Kinematic measurements: Wrist acceleration, reaction time
- Neurophysiological measurements
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    - Stimulus response curve (SRC) (Devanne et al., 1997)
    - Resting motor threshold (rMT) (Rossini et al., 1994)

Device Information:

- Two Magstim 200 stimulators connected via a Bistim module (Magstim Company, UK).
- Rapid Magstim2002 (Magstim Company, UK).

Motor training: Participants will be seated in a comfortable dental chair with armrests that supports the entire arm, wrist and hand. During training, participants will quickly extend their hand at a pace of one extension every 5 seconds (0.2Hz) in response to an auditory cue. An accelerometer or gyrometer taped to the dorsum of the hand will record the movements of the hand during the training. The only difference between the training protocol used in the current study and the training protocol used in a previous study (Buetefisch et al., 2015) is that the training protocol of the current study will have more rest (non-active) time. The amount of rest time given will be determined in the pilot experiment. Depending upon the amount of rest time provided, the training protocol could take up to 45 minutes.

Transcranial magnetic stimulation (TMS): We will apply repetitive TMS (rTMS) during motor training with an air-cooled figure-of-eight rTMS coil (7.0 cm diameter). To collect neurophysiological measurements, we will apply single- and paired-pulse TMS through a figure-of-eight TMS coil (7.0 cm diameter) using two Magstim 200 stimulators connected via a Bistim module (Magstim Company, UK). Both TMS coils will be registered to the participant's head using a frameless neuronavigation system (BrainSight software, Rogue Research, Montreal, Canada). The hotspot locations will be marked on a reconstructed MRI image of a "dummy" brain. This will permit us to maintain accurate positioning of the coil over the participant's skull and re-stimulate cortical locations across multiple study days with high precision. We will position TMS coil with the handle pointing backward and at a 45-degree angle with the midline

to induce an electrical current running posterior to anterior perpendicular to the central sulcus (Mills et al., 1992). The ECU M1 hotspot is the cortical area that, when stimulated with TMS, produces the largest MEPs in the ECU (Buetefisch et al., 2015).

Five rTMS protocols will be administered during motor training. Subjects will receive only one protocol each training day. The protocol order will be randomized for each subject prior to recruitment. Each protocol will administer less than 360 TMS stimuli in total. All protocols will administer TMS over either the motor cortices or over the somatosensory cortex at 90% (subthreshold) of the resting motor threshold (rMT) with a frequency of 0.1Hz.

Neurophysiological measurements: We will use Parametric Estimation by Sequential Testing (PEST) to determine the rMT (Mishory et al., 2004). The mathematical algorithm implemented by PEST will allow us to determine the rMT with fewer TMS pulses than the traditional EMG method (Rossini et al., 1994). We developed a separate LabView program (National Instruments, USA) to control the timing of each TMS protocol (repetitive-, single-pulse and paired-pulse TMS). All TMS protocols agree with current safety guidelines (Wassermann, 1998; Rossi et al., 2009).

We will use a single pulse TMS protocol to acquire a stimulus response curve (SRC) before and after motor training (Buetefisch et al., 2015). A SRC is a set of MEPs collected in response to TMS pulses of increasing intensities that can be used to characterize input-output parameters of the corticospinal tract (Devanne et al., 1997). We will apply less than 100 TMS stimuli to the motor cortex during the acquisition of a SRC although the exact number depends upon the resting MT of the participant. The TMS intensities used will range from 5% maximum stimulator output (MSO) below the resting MT up to 80% MSO. We will progressively increase the TMS intensity in increments of 5% MSO and 10 TMS stimuli will be applied at intensity.

We will use a paired-pulse TMS protocol to evaluate short-interval intracortical inhibition (SICI) of M1 before and after motor training (Kujirai et al., 1993b). We will apply 20 pairs of stimuli and 14 single stimuli, interspersed. During paired stimulation, a sub-threshold conditioning stimulus (CS) will precede a supra-threshold test stimulus (TS) by 2 ms. The intensity of the test TMS stimuli will be 120% of resting MT. The intensity of the conditioning TMS stimuli will be either 60% or 80% resting M1 (10 each). Of the single stimuli, the intensity of 10 stimuli will be 120% resting MT and the intensity of 4 stimuli will be 80% resting MT.

Surface electromyographic (EMG) activity of the extensor carpi ulnaris (ECU) and flexor carpi ulnaris (FCU) will be collected in a belly-tendon montage and a data acquisition system (LabView, National Instruments, CA, USA). Tin 9mm diameter surface electrodes will be placed in a belly-tendon montage on the skin overlaying the ECU and FCU of the training arm. The EMG activity will be sampled at 5kHz, amplified, filtered with a bandpass 1Hz – 1kHz, digitized and stored on a PC for offline analysis.

Kinematic measurements: To evaluate the changes the kinematics of the wrist extension, we will ask participants to perform 7 auditory-cued ballistic wrist extensions before (pre) and immediately (post), 30 minutes and 60 minutes after training. A two-dimensional accelerometer or gyrometer will be taped to the dorsum of the training hand to record the movement of the wrist. We will also record the activity of the ECU and FCU muscle during the ballistic extensions using EMG. To quantify reaction time, we will use a Labview program (National Instruments) to determine the length of time between the auditory cue and the onset of the movement-related EMG burst of the ECU.

STATISTICAL METHODS

A software program (LabView, National Instruments, CA, USA) will record and store acceleration andEMG on a PC for offline analysis. We have developed LabView programs to extract the peak acceleration and reaction time of each extension. We will perform separate repeated-measures ANOVAs to determine significant changes in maximum wrist acceleration and reaction time from before training (pre) to after training (post, 30 min., 60 min.) for each rTMS protocol. The maximum wrist acceleration and reaction time will be the dependent variable and time of measurement (pre, post, 30 min., 60 min.) will be the independent variables.

We will calculate the mean peak-to-peak MEP amplitude elicited by each TMS intensity to construct four SRCs (pre, post, 30 min., 60 min.) from each testing day for each participant. We will use statistical software (JMP, SAS Institute Inc., Cary, NC) to fit the mean SRC to a three-parameter sigmoidal function with a Levenberg-Marquard algorithm. The algorithm will allow us to determine the recruitment rate and maximum output from the stimulated cortical area (Devanne et al., 1997). We will test the effect of the different rTMS protocols on SRCs using repeated-measures ANOVA. MEP amplitude will be the dependent variable. Time of measurement (pre, post, 60 min), rTMS protocols 1-5, and TMS intensity will be the independent

variables. To measure intracortical inhibition, we will calculate % change in MEP amplitude of the TS when the TS is preceded with the CS in paired-pulse TMS (Buetefisch et al., 2015). To evaluate the effect of the TMS interventions on intracortical inhibition, we will perform repeated-measures ANOVA with % MEP amplitude as the dependent variable and time of measurement (pre, post, 60 min.), intensity of stimulator output, and rTMS protocol 1-5 as the independent variables. Subject will be the random factor. An alpha level of 0.01 will correct for multiple comparisons.

DATA SAFETY MONITORING PLAN

The proposed research will include human subjects. Prior to participation, subjects will complete informed, written consent that will describe the study protocol, payment, confidentiality and risks associated with our study. If new information becomes available on the risks associated with TMS, EMG or our motor training, participants will be re-consented.

Transcranial magnetic stimulation: Participants must complete a TMS safety screener (Rossi et al., 2009) and be approved by the investigator's advisor (Dr. Cathrin Buetefisch, MD, PhD) before participating in the study. Dr. Buetefisch is a board certified neurologist and has over 15 years of experience working with TMS. Participants will be required to sign the TMS safety screener to confirm they do not metal in their upper body or an implanted medical device (such as a cochlear implant, neurostimulator or pacemaker). Furthermore, participants will be disqualified if they have a history of epileptic seizures or have experience head trauma associated with a loss of consciousness/concussion. The single-pulse TMS, paired-pulse TMS and rTMS protocols used in this study agree with published safety guidelines and pose minimal risk to human health (Wassermann, 1998; Rossi et al., 2009). The TMS frequencies of the proposed study (0.1 Hz, 0.2 Hz) are reported to have no effect of cortical excitability (Chen et al., 1997) and are, therefore, well below the risk of inducing a seizure (Wassermann, 1998). TMS can cause discomfort if facial nerves and muscles on the scalp are activated (Rossi et al., 2009). To minimize discomfort, subjects will receive the full range of TMS intensities during an inclusion experiment and will not qualify for the study if they cannot tolerate one or more TMS intensities.

Adverse Event: In the unlikely event of a serious adverse event fitting the description of life threatening, hospitalization (initial or prolonged), disability/incapacity, intervention to prevent permanent impairment/damage or death, the event will be reported to the IRB

immediately upon knowledge of the event. In addition, the event will be investigated, and after consultation with the IRB, a decision may be made to terminate the study. All experiments will be conducted on the 2nd floor of the Center for Rehabilitation of Emory University. This location is in close proximity to the medical center at Emory University and ensures that medical care is easily accessible for our subjects in case of a medical emergency. The investigator's advisor, Dr. Cathrin Buetefisch MD, is also a board certified neurologist and will supervise all experimental sessions. A flow chart with the phone numbers to use in case of an emergency is located on the wall above the phone in the lab. The PI will be responsible to report all adverse events to the IRB in the annual report.

Confidentiality: We will protect the identity of our subjects by assigning each subject a study number. All data will be identified with the study number instead of identifying information. We will store the information that links the study numbers to the participant names in a locked file cabinet in our research office. Participants will be informed during the consent process of the circumstances (audit, court order, ect.) to when their identifying information may be accessed. The offices that may need access to identifying information include the Food and Drug Administration, the Office for Human Research Protections, the sponsor(s), the Emory Institutional Review Board, the Emory Office of Research Compliance and the Office for Clinical Research.

Participation/withdrawal: Participation in the current study is completely voluntary. Participants have the right to withdraw their participation at any time. There is no alternative to participation other than withdrawal.

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