Using TMS to Increase Executive Function in Older Adults

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Study Protocol

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Behavioral research on aging has mapped contrasting patterns of decline and stability in cognition across the adult lifespan. Both cross-sectional and longitudinal studies find robust declines in working memory (WM), which describes the storage and manipulation of temporary representations of information that was just experienced or just retrieved from long-term memory. The current proposal seeks to use a functionally-guided brain-stimulation (repetitive transcranial magnetic stimulation or rTMS) paradigm to modulate the working memory functions of the left dorsolateral prefrontal cortex (DLPFC) or left parietal cortex (PC). The research team carries the expectation that, active rTMS over the DLPFC and PC will improve WM perfomance compared to sham rTMS; and since older adults rely more heavily on prefrontal function than young adults, older adults will benefit more from DLPFC stimulation than the young. Differential rTMS modulation of WM performance between young and older groups will provide causal evidence for compensatory processing, and help fill out our understanding of the neural basis of sustained, successful performance in aging. While we have previously demonstrated WM effects from stimulating the lateral occipital cortex (LOC), a specific region within the occipital PC, a finding of relative enhancement of executive processing with PFC stimulation- an enhancement that is long lasting and that transfers to executive processing beyond WM- is a key to development of noninvasive brain stimulation treatment of cognitive deficits, as this more frontal brain region is closely associated with neuroplastic abilities like executive processing. This will be tested through three aims, in which rTMS will be applied over the DLPFC (Aim 1a), the LPC (Aim 1b) or both the DLPFC and the LPFC in alternating blocks (Aim 1c). We have 3 key objectives:

Primary Objective: To evaluate the ability of rTMS applied to the DLPFC, the PC to enhance working memory performance in both younger and older adults.
Primary Endpoint: We expect performance enhancements between active and sham rTMS to PFC or PC to increase as the task becomes more difficult, as executive control processes are centered in this region.

Design and Procedures

This blinded, sham-controlled trial will feature a mixed model cross-over design, with rTMS Type (active, sham), Difficulty Level, Stimulation Location (DLPFC, PC), and Group (Young, Older adults) as factors. As such, this design reflects the fact that all subjects receive both active and sham rTMS applied to up to two different scalp locations during a WM task at up to three levels of difficulty. Study procedures are listed in **Table 1**. Up to thirty healthy young adults (age range: 18-35 years), thirty healthy older adults (age range: 55-80 years), will participate. In the initial session, which will take about 3 hours, participants will be consented and screened for the study, have a saliva sample taken, have TMS motor threshold determined, and then learn and practice the WM task. A structural and functional MRI will then be acquired within the screening visit or in a separate visit dependent on the participant's schedule. Cortical locations within PC and PFC to be used as targets for rTMS will be chosen from an analysis of subject-specific fMRI activations. Following the MRI, participants will take part in up to 5 sessions of rTMS (4 visits in Aim 1 and Aim 1b; and two visits in Aim 1c), each lasting up to 3 hours. TMS sessions will begin ~1 week after the MRI Session, to allow for time to process the imaging data, and within a 3-month period (Mondays thru Fridays), aiming to occur at the same time each day (+/- 2-3 hours for scheduling flexibility). Up to 5 rTMS sessions (involving active or sham rTMS and DLPFC (Aim 1a, Aim 1c), or PC targets (Aim 1b, Aim 1c) will use coil locations and rTMS device intensities based on realistic head modeling. Participants will report number of hours slept the previous night at each visit.

Table 1. TIMELINE OF STUDY PROCEDURES FOR MAJOR STUDY:

Assessment	Screening Session	MRI Session	rTMS Sessions
1. Subject consent & screening	X		
2. Practice with WM task	X		
3. Structural MRI	(X)	X	
4. fMRI with WM task	(X)	X	
5. Motor Threshold	X		
6. WM task + rTMS			X
7. Side Effect Checklist			X
8. Visual Analog Scale			X

Subject Screening

Normal right-handed volunteers will be recruited from the community. At the beginning of their first visit to the rTMS laboratory, they will undergo neuropsychological screening (such the MINI, NACC, PHQ-9, CDR and/or BDI) and a urine test. If they pass the screening procedure, they will proceed to the rTMS lab, where

they will learn and practice the memory tasks used in the study (about 2 hrs), and will have a short session of rTMS (about 0.5 hr), in order to acclimate them to rTMS and to obtain right and left hand motor thresholds for future dosing of rTMS.

WM TASKS:
Two WM tasks will be performed a Delayed Response Alphabetization task (DRAT, Aim 1a, 1b, 1c) involving both maintenance and manipulation of information and a Delayed Response Maintenance Task (DRMT, Aim 1c) that only involved maintenance. Our implementation of the WM task for MRI consists of up to 10 runs of approximately 10-minute long letter-presenting blocks. Each trial begins with the presentation of a fixation cross during 5 seconds followed by the presentation of up to 9 uppercase letters arranged in a line. In the case where fewer letters are presented, all other positions are filled with asterisks. Stimuli are presented for up to three seconds before the screen is cleared. After a retention interval of 5 seconds, a probe stimulus is presented in the center of the screen for four seconds. The probe consists of the combination of a letter and a number, and which subjects are asked to answer. During this period subjects must press one of three keys indicating whether the number matches the position of the letter in the reorganized alphabetical order for the DRAT; or the serial position of the letter for the DRMT (Valid trials); or if the number does not match the letter position (Invalid trials); or if the letter did not belong to the array of letters (New, Aim 1a and 1b). Feedback is provided, at the end of each block as the overall accuracy. Tasks are performed with 1 (Hard, Aim 1c first cohort), 2 (Easy and Hard, Aim 1b and Aim 1c second cohort), or 3 (Easy, Medium, and Hard: Aim 1a) difficulty levels, defined as the number of letters presented on the screen and individually for each subject according to their performance during the screening visit. In rTMS sessions, the WM tasks will be run while stimulation is applied over the DLPFC (Aim 1a, Aim 1c) or the PC (Aim 1b, Aim 1c) either before the encoding (Aim 1a, Aim 1c) or during the delay period (Aim 1b, Aim 1c). Each block of trials will take about 10 minutes. To clarify all these conditions please refer to Figure 1 below.

	Group	Dosing	Timing	Site	Task	Difficulty	
Aim 1a	YA OA	100%rMT 100%Eref 80%Eref	Before the encoding During the delay	Frontal Parietal	DRAT DRMT	Easy Medium Hard	n= 29YA + 18 OA (6conditions/subj)
Aim 1b	YA OA	100%rMT 100%Eref 80%Eref	Before the encoding During the delay	Frontal Parietal	DRAT DRMT	Easy Medium Hard	n= 15OA (4conditions/subj)
Aim 1c *Cohort 1*	YA OA	100%rMT 100%Eref 80%Eref	Before the encoding During the delay	Frontal Parietal	DRAT DRMT	Easy Medium Hard	n= 15YA (4conditions/subj)
Aim 1c *Cohort 2*	YA OA	100%rMT 100%Eref 80%Eref	Before the encoding During the delay	Frontal Parietal	DRAT DRMT	Easy Medium Hard	n= 14YA (8conditions/subj)

Figure 1: Condition used for each sub-aims of the study, the highlighted cells represent the conditions used for each subaims.

MOTOR THRESHOLD DETERMINATION:
All rTMS procedures will occur in the Noninvasive Neuromodulatory Neuroscience (N3) Lab in rooms 54211 and 54212 in the Department of Psychiatry and Behavioral Sciences, Duke Clinic South. Motor threshold (MT) is defined as the minimum magnetic flux needed to elicit a threshold EMG response in a target muscle in 5 out of 10 trials. MT is the standard in the field for determining the intensity of rTMS for each individual 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 initiated by the MUSC PEST program.

MT will be determined for one or both hemispheres with the muscle at rest (verified by baseline EMG). Individual MT will be used to determine the intensity of stimulation for each individual, as recommended by safety guidelines.

MRI/FMRI PROCEDURE:
At BIAC, after obtaining a structural MRI and DTI and resting-state fMRI scans, fMRI data will be recorded from subjects while they perform the WM task. BOLD images will be acquired with a 3.0T GE MR Scanner. Stimuli will be back-projected onto a screen located at the head of the MRI bed using an LCD projector. Subjects will view the screen via a mirror system located in the head coil. Task onset will be electronically synchronized with the MRI acquisition computer. Task administration and collection of RT and accuracy data will be computer controlled. The scanning session will take about 1.5 hr.

Studies will be using a GE Premier Performance 3T MRI scanner, which is an improved version of GE's FDA-approved Premier system, but with better capabilities for high-resolution imaging. All operational parameters on this improved system will be within FDA guidelines to meet the same minimal risk device criteria and ensure safety of human subjects. As such, an Investigational Device Exemption (IDE) is not necessary. The research conducted under this protocol is not to evaluate the safety and efficacy of this device.

APPLICATION OF RTMS DURING WM TASK PERFORMANCE:
The subject will be seated comfortably in a chair, facing a computer screen positioned in front of the subject for visual stimulus presentation. Earplugs will be worn to protect hearing. The participant's head may be held steady by a frame with a chin rest and the rTMS coil holder frame. A figure eight magnetic coil will be placed on the scalp and held in place with a coil fixing system supplied by MagVenture. This will be paired with the BrainSight tracking system which provides precise fMRI-guided rTMS coil placement for basic, translational, and clinical applications of rTMS. The BrainSight program enables the coil to be placed at precise cortical targets (chosen from the subject's fMRI activations from the WM task from the MRI session) on the individual's 3-dimensionally rendered brain MRI with less than one millimeter error, and enables the research team to dynamically move the coil to account for slight head movements while the subject performs the task. Five-second trains of 5 Hz rTMS will be administered at up to 130% of the individual's MT with the stimulating coil tangential to the scalp. Sham rTMS will be administered with a sham coil equipped with shielding to block magnetic field output but retain the auditory and some of the tactile aspects of active stimulation. rTMS administration will be controlled by an external computer and will be time-locked relative to stimulus presentation. A brief rTMS side effect rating scale and visual analog mood ratings will be administered before and after each rTMS block. There will be up to 12 blocks of trials per session, and each session will take about 2 hrs. Subjects' side-effects will be monitored closely. As indicated in the procedures section, side effects are assessed in a charted, structured interview both prior to and after the rTMS session. Subjects are instructed during the consent process and during the rTMS sessions about all known side effects. They are further instructed during consenting and additionally at the conclusion of the rTMS session to contact the principal investigator or study physician with any questions or concerns (including those that may arise after the experimental session has ended).

Imaging acquisition and preprocessing. Three forms of structural images will be acquired: **1) full-brain high-resolution T_1-weighted structural images** (inversion recovery prepared 3D SPGR) with full coverage of the head and neck, (TR = 500ms; TE = 20ms; FoV = 24cm^2; image matrix = 256x256; voxel size = 0.94 x 0.94 x 1mm), and **2**) **echo-planar (EPI) sensitivity encoding (SENSE) DWI images** with the same orientation (TR = 2000 ms; FoV = 24 cm^2; image matrix = 128^2; voxel size 0.94 x 0.94 x 1 mm; b-value = 1000 s/mm^2; 1 repetition; 36 diffusion-sensitizing directions). In addition, two forms of functional images will be collected: 1**)** for **resting state EPI** functional imaging data, which will be used to estimate RSFA, we will acquire 24 slices parallel to the AC-PC plane using a BOLD-sensitive gradient-echo sequence with EPI k-space sampling, at TR of 2s (TE: 35ms; FOV: 25.6cm; voxel size: 63mm), and 2) **event-related EPI**, which uses the same scan parameters and will measure the global reactivity to our Working Memory Task.

TMS methods. Coil targeting will be achieved using frameless stereotaxy (BrainSight: Rogue Research, Montreal). TMS is applied with a figure 8 coil based on 100% resting motor threshold (rMT), though TMS intensity will also be informed by E-field modeling (described below). TMS will be delivered consecutively over the individualized target region, based on the cortical site with the highest computed controllability (Network target) or parametric activity (Activity target), using a MagVenture stimulator. Neuronavigation (BrainSight, Rogue Research, Canada) and a robot (SmartMove, ANT, Netherlands) will be used to optimize the targeting. Brain atrophy could also reduce TMS effectiveness because it increases the distance between scalp and the cortex but this potential confound is addressed by adjusting TMS intensity using the E-field computation. In visits 3 to 6, participants will perform the Working Memory Task while active or electrical sham stimulation is delivered using an A/P Cool-B65 coil (MagVenture, Denmark). In a stimulation trial, twenty-five pulses of 5Hz

rTMS will be delivered at 100% of the effective E-field. Sham rTMS will be administered with a sham coil equipped with shielding to block magnetic field output but retain the auditory and some of the tactile aspects of active stimulation. This method reproduces the somatosensory sensations as the magnetic field stimulates scalp muscles, and produces the same acoustic artifact than the active stimulation, without inducing current in the cortex.

E-field Modeling. In order to determine the *intensity* of network-based targeting, we will use electric field (E-field) modeling. The BSEL lab has extensive experience with the creation of anatomically realistic E-field models of transcranial electric and magnetic stimulation in humans, which have been applied to healthy OA populations in ongoing NIH-funded projects by Co-I's Cabeza and Appelbaum (U01-AG050618), using SimNIBS software[63]. A detailed model of the TMS coil is combined with a detailed head model. Isotropic tissue conductivities are assigned to the various tissue compartments. Critically, this method will also include anisotropic conductivity in the white matter based on the DWI data. We will carry out E-field simulations over a range of coil orientations and tilts to predict maximal activation of the FPN. The target node (i.e., the node with the highest controllability, identified above) will be used as the center of a 3×3 grid for positioning the coil in simulations of the E-field corresponding to these 9 coil positions and 6 orientations (54 combinations). The simulation E-field maps will be extracted and correlated, voxel-to-voxel, with the fMRI activation and the simulation that yields the highest correlation is selected as the target coil position and orientation.