Using fMRI-guided TMS to Increase Central Executive Function in Older Adults (MCI_Sub)

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This document includes the study protocol and the statistical plan approved on March 1st 2020.

Study Protocol:

This experimental supplement is focused on applying TMS to a cortical network node in 30 patients diagnosed with MCI or found to be at risk for cognitive impairment (This cohort will be referred to as "MCI patients", but includes subjects with diagnosed MCI and subjects not currently diagnosed, but at risk for cognititve impairment as defined by criteria below)**.** This blinded, sham-controlled trial will feature a mixed model 2 x 3 x 2 x 2 cross-over design, with rTMS Type (active, sham), Difficulty Level defined by accuracy (easy, medium, hard levels), Stimulation Location (Network, Activity target), and Group (healthy OAs, MCI) 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 3**. Thirty healthy OAs (age range: 55-80 years) and thirty MCIs (age range: 55-80 years) will participate. In the first session, which will take about 2 hours, participants will be consented and screened for the study, submit a saliva sample for genetic testing, determine TMS motor threshold, and then learn and practice the WM task. The next visit will involve a structural MRI and fMRI recorded from both groups while they perform the WM task. Cortical locations within the FPN (Network target) and DLPFC (Activity target) will be used as targets for rTMS will be chosen from an analysis of subject-specific fMRI activations from the WM task completed in this MRI Session. This session, which will last up to 3 hours, will be followed by up to four sessions of rTMS + MRI, each lasting about 3 hours. These rTMS+MRI sessions will begin ~1 week after the MRI Session, to allow for time to process the imaging data. rTMS+MRI sessions (involving active or sham rTMS and Network or Activity targets) will use coil locations and rTMS device intensities based on realistic head modeling the MRI will collect structural and resting state information.

***Working Memory task*.** In order to test for cognitive performance differences in response to TMS, we will rely on a validated WM task that has shown (1) reliable univariate activity in response to parametric increases in set size or load, 2) multivariate connectivity increases in response to load, and (3) reliable deficits in MCIs using similar stimuli and paradigms. Each trial comprises a set of presented words. On "rehearse" trials, individualssubvocally rehearsed a list of words across a memory delay. On "reorder" trials, individuals mentally rearranged a list of words based on the weight of the objects that the words referred to. Individuals are then probed on the correct order or position of a random word from the array. After scanning, individuals administered a surprise LTM recognition test on words processed in both conditions.

Stimuli in this experiment consisted of 504 words selected from the Medical Research Council Psycholinguistic database (**http://www.psych.rl.ac.uk/MRC_Psych_Db.html**). The words are 2–13 letters in length and moderate frequency, highly concrete, and highly imageable. These words were used to construct three separate lists of 168 words matched for length, frequency, concreteness, and imageability. Two of the word lists were used for the WM tasks, whereas words from the third list were used as foils for the subsequent LTM recognition test. For the two WM word lists, unique word triplets were constructed in a psuedo-randomized manner. The authors inspected the triplets to ensure that there was no ambiguity in terms of the relative referent weight or pronunciation of the words. The two WM word lists were counterbalanced between subjects and WM condition.

SALIVA SAMPLE: A saliva sample will be obtained from healthy volunteers and MCI patients in this cohort and will be used to perform APOE genetic testing, a risk marker for Alzheimer's Disease. Samples will be obtained by administration of a cheek swab and stored in a secure environment. Subject samples will be deidentified and labeled with the subject study number. Genetic testing will be performed at the Biofluids Shared Resource.

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)[58], 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[59].

DWI Structural Connectivity. *Whole-brain tractography.* As in our prior DWI tractography work, Dipy[60] will be used to generate connectomes representing structural connections between all cortical regions in the Harvard-Oxford Atlas. For structural connection matrices, network edges are defined by the number of tractography streamlines between all nodes of the target network.

Event-related fMRI analyses, functional connectivity and graph theory measures. The Frontoparietal network (FPN) is identified by standard atlas[61], and will be validated with voxelwise independent component analysis (ICA). Task-related connectivity is measured using beta-series correlations[20], which estimates a time-series by examining region-by-region interactions that are modulated by task conditions. SMEs for activity and connectivity will be analyzed with a Group (healthy OAs vs. MCIs) x Targeting (Network-based vs. Traditional) x Stimulation (Active vs. Sham) ANOVA using SPM[62]. All matrices are evaluated for descriptive graph-theoretical properties (including degree and controllability) using the Brain Connectivity Toolbox.

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.

Statistical Plan:

Power analysis. Our labs have considerable experience with combining neurostimulation and neuroimaging. Through the parent award we have enrolled 85 individuals in multiday memory protocols and results from these data reflect the size of potential future TMS effects. Power calculations were therefore conducted in R software (R Development Core Team, 2016) using the repeated-measures ANOVA module. With N=80 subjects, in a mixed-effects design consisting of 4 repeated measurements per subject (2 groups x 2 TMS targeting [network-based, traditional targeting), Cohen's d = 0.9 for each of the main effects, with interaction effects between 0.7-0.9, attaining an average power of 0.8 at an overall significance level of 5%.

Analytical Rigor. In our analysis phase, we will ensure scientific rigor in the following ways. To address bias in ANOVAs due potential violation of the sphericity assumption in Studies 1 and 2, we will estimate sphericity and correct for this bias using a Greenhouse-Geisser correction. In order to ensure replicability in our findings, we will report analytical procedures according to the Committee on Best Practice in Data Analysis and Sharing (COBIDAS) report for fMRI data analysis. Finally, to ensure generalizability of our findings, we will perform a k-fold cross-validation on all fMRI data analyses. In k-fold cross-validation, the data is divided into k independent subsets. On each fold, one subset is held out as the test set, the others are used for training. Empirical studies suggest that choices of k in the range of 5 to 10, yield good results in practice.

Consideration of sex as a biological variable. We will fulfill this recent NIH mandate by including both sexes in the research and by including gender as a covariate of interest in all analyses. Because this is an exploratory study, we have no a priori predictions on how gender might influence the TMS-imaging results. Although we may be underpowered to observe sex differences, the outcome of this Administrative Supplement can be used to estimate effect sizes to adequately power gender differences in future larger-scale studies.