TMS in Primary Progressive Aphasia: Modulation of Brain Networks and Language

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SYNOPSIS

Project title: TMS in Primary Progressive Aphasia: Modulation of Brain Networks and Language

Objective: The objective of this study is to assess the potential transient and durable benefits of repetitive transcranial magnetic stimulation (rTMS) to behavior and brain network in the three variants of Primary Progressive Aphasia (PPA): logopenic, semantic and nonfluent PPA.

Study Period:

Planned enrollment duration: 30 months

Planned study duration: 3 months per participant

Number of Patients: 10

Study Intervention:

Repetitive transcranial magnetic stimulation (rTMS) has emerged as a potential treatment option for Primary Progressive Aphasia. rTMS can induce long-term plastic changes and selectively alter functional network connectivity, which may improve symptoms related to language and cognition. In this study, resting state functional MRI (rsfMRI) is used before rTMS to localize an individually optimized target for stimulation, and after rTMS to measure effects of stimulation on network functional connectivity and language.

Experimental Design:

This study follows a double-blinded, placebo-controlled, cross-over experimental protocol. Participants are randomized to start with either active or sham rTMS during 10 weekdays (Monday through Friday), over 2 consecutive weeks. Intervention arms are separated by a four-week washout period. Language assessments, MRI assessments, and questionnaires are included at the baseline timepoint and after the end of both active and sham arms. A follow-up timepoint including a language assessment is conducted three weeks after the end of Arm 2.

Inclusion criteria:

1. Between the ages of 40-99
2. All participants are native English speakers

3. Willing and able to consent to the protocol and undergo imaging and neuropsychological testing at the specified time points
4. Patients with very mild or mild PPA are included.

Exclusion criteria:

1. History of head trauma involving loss of consciousness or alteration in consciousness
2. Another major neurologic or psychiatric condition
3. Known presence of a structural brain lesion (e.g. tumor, cortical infarct)
4. Any contraindication to MRI, such as presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments, or foreign objects in the eyes, skin, or body
5. Longstanding premorbid history (i.e. longer than 10 years) of alcohol or substance abuse with continuous abuse up to and including the time that the symptoms leading to clinical presentation developed
6. Any significant systemic illness or unstable medical condition which could lead to difficulty complying with the study protocol.
7. Unwilling to return for follow-up, undergo neuropsychological testing, TMS, and MR imaging
8. History of unprovoked seizures (i.e., seizures that occur in the absence of a clear provocation such as hyponatremia, hypoglycemia, etc.).
9. Subjects who have a first degree relative (e.g., father, mother or sibling) with a seizure disorder.
10. Subjects currently taking, or plan to take, medications which are highly epileptogenic. These include clozapine, high doses of bupropion (i.e., greater than 400mg daily), diphenhydramine, cyclosporine, isoniazid, imipenem, chloroquine, tramadol and theophylline.
11. Subjects actively on anti-amyloid treatments.

Equipment:

MRI: scans acquired using a Siemens 3.0 T whole-body Siemens MRI scanner housed at the Athinoula A. Martinos Center for Biomedical Imaging at the Massachusetts General Hostpial, Charlestown Navy Yard. All MRI scan sessions last 30-60 minutes. During MRI scanning patients lie supine in the MRI machine. Patients' heads are fitted with pillows and cushions to reduce motion artifact and are given earplugs to protect their hearing. Patients are given a "squeeze ball," which they can compress at any time if they are feeling uncomfortable or if they wish to be removed from the scanner. Study staff periodically ask patients if they are feeling well.

MRI sequences include brief localizer scans, field-mapping sequences, high resolution anatomical scans, and functional MRI blood oxygenation level-dependent sequences (BOLD).

TMS: rTMS is administered with a MagPro X100 stimulator (MagVenture, Denmark), using a 70 mm figure-of-eight liquid cooled coil capable of doing active or sham stimulation (e.g. the Cool B65 A/P coil).

The target for rTMS is in the left dorsolateral prefrontal cortex. Accuracy and reproducibility of targeting is achieved with a frameless stereotactic optical tracking neuronavigation system (e.g. Brainsight™ or Localite), which permits real-time monitoring of coil placement and head position. Sham stimulation is delivered to the exact same cortical targets. While no electromagnetic stimulation is delivered during sham, the sounds will approximate active stimulation, and skin electrodes will approximate the sensation of active rTMS.

For all sessions, rTMS is delivered at 80-120% of a patient's resting motor threshold. The resting motor threshold is determined by the minimal stimulus intensity to elicit movement of the contralateral first dorsal interosseous muscle-or to elicit a motor evoked potential (MEP) of at least 50μV-on three out of six trials. rTMS is administered in an excitatory pattern as intermittent burst stimulation (iTBS) (bursts of 3 pulses of 50Hz rTMS). Parameters are well within established safety guidelines (Rossi et al. 2009).

Primary outcomes:

Language Performance: The primary outcome is the change in language performance as measured by Boston Naming Test (BNT) before and after TMS.

Brain network connectivity: The main neural outcome measure is the relative change in z-transformed correlation coefficients between regions of the language brain network before and after TMS.

Statistical Analysis:

Language performance: A within-subjects repeated measures ANOVA is used to compare the change in language performance following active rTMS condition versus the sham stimulation condition.

Brain network connectivity: A within-subjects repeated measures ANOVA is used to compare the change in language brain network functional connectivity following active rTMS condition versus the sham stimulation condition.