Effects of Transcranial Direct Current Stimulation (tDCS) on Language

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Study Protocol

Background:

Aphasia is a disturbance of language, primarily caused by brain injury to the left cerebral hemisphere. Aphasia treatments include speech and language therapy and pharmacologic therapy, but several studies have found that these treatments are not completely effective for patients with aphasia, leaving them with residual deficits that significantly add to the cost of stroke-related care. Additionally, the amount and frequency of speech and language therapy delivered may have a critical effect on recovery. Therefore, there is a need for new treatments or adjuncts to existing treatments, such as brain stimulation interventions, that have the potential to show greater improvements in patients with aphasia. One such new approach for non-invasive brain stimulation is transcranial direct current stimulation (tDCS).

This study will examine the effects of tDCS during speech therapy to further examine which method or methods is best for patient recovery. Patients enrolled in the study will undergo language testing that covers a broad range of language functions. Functional Magnetic Resonance Imaging (fMRI) will be completed before and after speech therapy intervention arms to investigate the neural processes affected by tDCS and speech therapy.

Aims:

Aim 1: In a group of patients with aphasia, identify what specific language processing impairment they have after stroke (i.e. phonologic, semantic damage) and assess whether targeted phonologic or semantic speech therapy intervention on the damaged process with perilesional (targeted) vs. active control tDCS is most beneficial for recovery.

Aim 2: Collect resting-state fMRI before and after tDCS to examine the neural processes that are affected by tDCS.

Methods:

Inclusion Criteria

Patients must be 18 or older.
Patients may not be older than 85.
Patients must have a language deficit from focal neurologic damage (e.g. stroke, tumor).
Patients must be adults and have English-language fluency.
Patients must be eligible to undergo MRI.

Beyond meeting the inclusion criteria, no preference will be given on the basis of race, ethnicity or gender.
Patients that have suffered cerebrovascular accidents will be included when they are in the chronic (>4 months post stroke) stage.

Exclusion criteria:
Advanced neurodegenerative disease (i.e. Stage 3 Alzheimer's disease) or neurologic disorder (e.g. idiopathic epilepsy not well managed by medication, Parkinson's disease, ALS)
Severe psychopathology (e.g. schizophrenia, bipolar disorder, acute major depressive episode)
Suspected or diagnosed uncorrectable hearing or vision difficulties, or developmental disabilities (i.e. intellectual disability or learning disability).
Contraindications to MRI such as claustrophobia, implanted electronic devices, MRI-incompatible metal in the body, extreme obesity, pregnancy, inability to lie flat, inability to see or hear stimulus materials.
Younger than 18 or older than 85.

Recruitment:
Flyers will be available for distribution in Froedtert Neurology and PM&R clinics. Advertisement will involve the same information on the flyer to be displayed on the FMLH or MCW website regarding clinical studies.
Flyers will also be distributed at local Universities, hospitals, rehab facilities, and assisted living facilities such as UW Milwaukee, MU, Aurora, and Ascencion. Each university/hospital/organization will be contacted for permission to post.
study is listed on clinicaltrials.gov and participants may contact study coordinator to learn more about study.
Participants will be recruited through referrals from area physicians and speech pathologists, and through advertisement on the MCW/Froedtert hospital website regarding clinical/research trials. Physicians and speech pathologists will provide study contact information to potential participants or will provide potential participants the opportunity to sign a release of information if they wish for their contact information to be forwarded directly to the study team for follow-up. The study team will describe to the participant the nature and requirements of the study.

Decisional capacity of the patient is clinically assessed by the referring physician and is routinely required for decisions regarding patient care. Decisional capacity will also be assessed by the consenting research staff during the consenting procedure. Decisionality assessment is based on determining whether the patient is oriented to self, location, and date; can understand communication well enough to grasp its essential meaning; and has insight and impulse control sufficient to choose alternatives that are in his or her best interest. If a patient's decisionality is in question, more in depth interview-based testing of the patient will be conducted by a clinical neuropsychologist. The patients will be asked to answer questions in

the "Aphasia Decisionality Questionnaire" to assess understanding of the study. If a patient is determined to be non-decisional for study purposes and enrollment, an authorized representative will be asked for informed consent; decisional ability is indicated by a score of 80% correct or better.

Finally, it is likely that there will be some participants who fall into the "vulnerable" categorization based on age and/or cognitive impairment and/or reading/language disabilities, given the populations being studied. For example, the average age of our participants will probably range between 55-65, but some participants may be 80 or older (and may be considered vulnerable due to their age). Furthermore, our patient population will have suffered some form of neurologic incident, and there is a probability that mild cognitive impairment could be associated with this. Our patients may have aphasia, which by definition is a reading/language disability. It should be stressed, however, that if a patient is unable to comply with the study procedures because of severe cognitive impairment or reading/language problems, then they will be excluded from the study.

The exclusion of non-English language speakers is unavoidable because test materials will be available in English only, and because combining results from subjects performing language processing tasks in primary and secondary languages is considered scientifically unsupportable.

Inclusion of children younger than 18 would require development and application of specialized training techniques and test materials, which would add significantly to the cost of the project. Very few children under the age of 18 experience neurologic incidents, such as stroke, making the likely return on this investment very small.

Patients will undergo language testing at 3 time points. Patients will complete neuronavigation on the Brainsight Neuronavigation system. This is a noninvasive procedure used to determine the optimal location in the brain for stimulation. Stimulation Procedures: High-Density-tDCS will be delivered via a battery–driven constant direct current stimulator (Soterix) using a 4x1 montage (1 central anodal electrode and 4 cathodal electrodes) arranged in a HD-cap.

Study design:
Patients will either receive SFA or PCA language treatment to focus on specific processing deficits. Participants will undergo language evaluation (Time 1) before being randomly assigned to one of 2 therapy groups and stimulation. Participants will repeat a short-battery prior to repeating therapy items to ensure items cannot be consistently named. They will then receive tDCS for 10 therapy sessions. Stimulation site will either be perilesional (targeted) or an active control site in the opposite hemisphere. They will complete an additional 10 speech therapy sessions. They will then complete a final behavioral assessment (same as Time 2) at the

completion of the treatment (Time 3). Participants will complete fMRI sessions at Time 1, 2, and 3.

MRI. Participants participating in fMRI will be comfortably positioned in the MRI scanner. A fMRI study will then be performed. Scanning will be performed on GE MR 3T scanners. Participants will undergo a 60 to 90-minute 3T MRI scanning session at 3 different times during the study, and may include T1-weighted anatomical scan, a T2-weighted FLAIR scan, diffusion MRI/ diffusion tensor imaging sequences, language-task based fMRI (described below), and resting-state fMRI scan (described below), lasting approximately 45 minutes. Scanning will use MRI safety approved hardware and head coils. During the language-task based fMRI, participants will complete tasks to measure language lateralization in order to understand how language dominance changes asa result of therapy and stimulation. The adaptive semantic matching paradigm is a block design with a language condition (semantic matching) and a control condition (perceptual matching) alternating in 20-s blocks (1 run; duration: 6:40). To avoid taskswitching demands, which can be challenging for some people with aphasia, a single task applies to both conditions: press a button to matching pairs. In the language condition, pairs of words are presented, and a match is defined as a pair of words that are related in any way, e.g. boy-girl, lizard-snake, grass-lawnmower, but not walnut-bicycle. In the control condition, pairs of false font strings are presented, and a match is defined as pair of strings that are identical (ΔΘδЂЧ-ΔΘδЂЧ, but not ΔΘδЂЧ-ЧΔЂЏΔ). The key contrast will be semantic matching versus perceptual matching. The adaptive rhyming judgment paradigm is similar except that the language condition is pseudoword rhyming judgment (e.g. foo-voo, mulky-tulkie, cypermollicle-waiperbollical), which loads heavily on phonological encoding. The key contrast will be rhyming judgment versus perceptual matching. Participants will complete a short breath hold for during a 4 minute resting state acquisition run.

Therapy Items:
Items selected for therapy will be pictures and words that cannot be reliable named on 2 separate occasions. 4 lists will be created for pictures and words each (8 lists total). 2 trained lists for each therapy cycle, 1 untrained list and 1 untested list. Standardized PCA or SFA will be administered with the trained lists, and pre-specified cues will be given if a participant cannot come up with a response. Participants will be told whether they are correct or wrong and told the correct answer if they provide an incorrect response.

Behavioral Assessment:
QAB 3 different forms
CETI, CCRSA, CES-D for qualitative recovery
Language measures given include things like picture naming, repetition, reading, verbal working memory, etc.

Statistical analysis:
For behavioral results, means and standard deviations between the therapy arms will be computed. T-tests and ANOVA will be used for between and within subject analysis to evaluate outcome.

FMRI image processing and statistical analyses are performed using the AFNI software package. Each time series of 3D images is registered to the first steady-state image, and the six translation and rotation parameters estimated during this process are saved for use as noise estimates in later analyses. Images contaminated by large residual artifactual transients are detected automatically using regression techniques and tagged for censoring in later analyses. Data sets are rejected entirely if more than 10% of images show such artifacts.
Task-fMRI. Deconvolution techniques to estimate the hemodynamic impulse response function associated with each trial type (control or semantic/phonological decision). In brief, the analysis requires a set of temporal input vectors coding the occurrence of each trial type. Input vectors specifying estimated head motions in six parameters are also provided as covariates of no interest. The deconvolution generates, for each voxel, estimates of the baseline, linear trend, contribution of each motion parameter, and amplitude and temporal profile of the hemodynamic response for each trial type. Each estimate is accompanied by a statistical parameter. General linear contrasts can then be performed comparing the responses for any combination of conditions. Activity during the semantic or phonological decision task will be compared to the tones task and a laterality quotient will be calculated (ie. activation in the left hemisphere - activation in the right hemisphere/total activation).
Resting state: Initial analysis pipelines will culminate in individual participant connectivity matrices derived from rs-fMRI. The analysis includes image registration and unwarping, controlled minimal smoothing, detrending and noise removal, registration to a surface template, and extraction of time series data for cortical and subcortical regions of interest. ROIs will be defined by the Glasser parcellation, which divides the cortex of each hemisphere into 180 regions based on anatomical and functional criteria. These ROIs will be combined with subcortical parcellations including the thalamus, basal ganglia, and cerebellum. Individual participant connectome matrices will be constructed by computing pairwise Pearson correlations between all parcel pairs, followed by Fisher z-transformation.