Cognitive remediation augmented with transcranial direct current stimulation (tDCS)

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I. PURPOSE OF PROTOCOL

The proposed study will test the feasibility and tolerability of transcranial direct current stimulation (tDCS) added to a cognitive remediation program in n=100 adults. For up to 60 cognitive remediation sessions, participants will receive 20 minutes of active tDCS stimulation (up to 4.0 mA, montage dependent on specific area of deficits to be targeted) while they complete the cognitive training tasks.

After initial assessment and training, participants will be assigned to complete the cognitive training and tDCS sessions at home using a remotely-supervised tDCS (RS-tDCS) protocol to provide telerehabilitation. If a participant does not meet criteria for at-home treatment, the sessions will be delivered in clinic.

We have extensively developed both our cognitive remediation and tDCS methods including the RS-tDCS protocol (initially at our former institution, Stony Brook Medicine), alone and in combination in adults with multiple sclerosis (MS) and Parkinson's disease (PD). In MS, we have demonstrated that a program of adaptive cognitive remediation (that will be used clinically in this study) leads to significant cognitive gains [2, 3]. We then demonstrated the feasibility of tDCS combined with cognitive remediation, using our RS-tDCS for at-home treatment [2]. As described below, we have used this protocol in >1000 sessions, finding very high rates of compliance and tolerability.

II. BACKGROUND

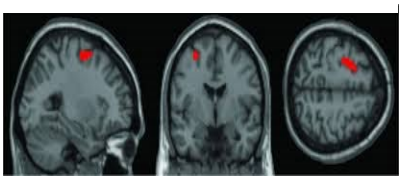
Cognitive remediation can lead to improved cognitive functioning across disorders. Cognitive training is an attractive alternate therapeutic option, especially in its online home-use format. Our group has demonstrated efficacy of this type of program for improving cognitive functioning in individuals with MS, training for 60 sessions across 12 weeks [3]. Preliminary data from our recently-completed randomized double-blind active-placebo controlled trials show that CT leads to greater gains in a neuropsychological testing composite z-score when compared to playing ordinary computer games (n=135, program by Posit Science[5], p=0.02, report in preparation; and n=20, program by Lumos Labs, 0.46 ± 0.59 improvement vs.−0.14 ± 0.48 decline, $p = 0.02$ [6]). However, the difference in average improvement of the composite z-score is relatively modest (n=135, z-score 0.20±0.36 vs. 0.05±0.31, p=0.02, Cohen's d =0.43). Further, we have developed a protocol to allow participants to cognitively train from home and shown its feasibility to use in a Multiple Sclerosis patient population [6]. The *remote access has resulted in rapid enrollment of >160 patients* in two years; in comparison, the largest published CT trial in MS (an outpatient memory training program with 10 sessions in five weeks) required *>7 years* to enroll n=86 participants[7]. Using our protocol we have found very high compliance (with no loss of study equipment). Such rapid enrollment emphasizes the tremendous unmet treatment need for people living with MS and other debilitating conditions, and has led to the established procedures to be used in this study to deliver remotely-supervised cognitive remediation.

Transcranial Direct Current Stimulation (tDCS) is a novel, safe, well-tolerated, and low-cost treatment approach that may enhance the benefits of cognitive remediation. The application of tDCS is a relatively recent therapeutic development that utilizes low amplitude direct currents to induce changes in cortical excitability [8-10]. tDCS is expected to produce neuronal polarization of less than one mV[11] and leads to relatively diffuse current flow, as demonstrated by imaging studies and computational models [12]. Most of the studies in healthy and clinical populations have used electrode montages that produce some current flow across the frontal lobe (including any montage with a supra-orbital "return"). A broad neuromodulation of the frontal pole may be consistent with a general mechanism of action for its activating effects, along with a general increase in large-scale network connectivity [13].

Though various non-invasive neuromodulation technologies are available (e.g., transcranial magnetic stimulation), tDCS has many advantages compared to other stimulation methods including ease of use, lower cost, and better tolerability (e.g., it has not been associated with development of seizures [14, 15]). tDCS produces current intensities in the brain orders of magnitude below other stimulation techniques such as transcranial magnetic stimulation (TMS) or electroconvulsive therapy (ECT) [16]; thus tDCS has none of the significant side-effects reported with these more intensive interventions. Many subjects feel nothing or only mild sensation during the main course of tDCS. Across studies, the most common side effect reported from this technique is a mild tingling sensation [9, 17, 18]. With an extensive record of safety and tolerability a recent safety review demonstrates that across trials, no serious adverse events have been reported and throughout the literature the most common side effects are specific to the electrode site and include mild itching, tingling, and burning [16, 18]. Initial studies have found tDCS to be effective in a variety of uses in healthy participants as well as in a range of clinical conditions [19-28] and may be preferred to drug treatment in special populations (such as pregnant women [29]) due to its safety advantages.

tDCS is considered especially promising for symptomatic treatment of neurological disease for its tolerability and, based on our innovative remotely-supervised approach, easy at-home use.
While there is emerging study of the cellular mechanisms of tDCS[30-33], what is established is that sustained (minutes) of tDCS can produce lasting changes in brain excitability[8-10] and that these changes are plastic and cumulative with repeated sessions [33]. One of the largest and more reproducible effects in healthy volunteers is enhanced vigilance with an increased ability to engage selective attention [17, 27, 34, 35], a finding which may indirectly underpin the cognitive benefits of tDCS.

Working Memory Cognitive Training



***Fig,1** :WM CT associated with increased perfusion of left precentral gyrus/frontal middle gyrus/superior frontal gyrus (from Buschkuehl et al. 2014)[1]*

+ DLPFC tDCS (OLE)

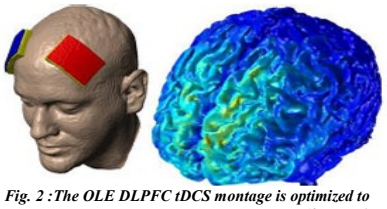


***Fig. 2 :The OLE DLPFC tDCS montage is optimized to targets similar regions for synergistic benefit** (from Seibt et al. 2015)[4]*

Pairing tDCS with cognitive remediation can improve training outcomes. While the programs in our studies were broadly successful, the training focused heavily on attention and working exercises (e.g., vigilance, n-back and span exercises) and we found the greatest benefits in this domain. Specifically isolating the working memory exercises, levels achieved within the CT system transfers to improvement on the representative working memory task, Paced Auditory Serial Addition Test (PASAT[36]) r=.33, p=.04, lending further support that targeted WM CT training boosts WM performance.

To meet this study's objectives, we will focus specifically on WM in both training and outcome. Limiting training to WM exercises will provide the opportunity to test proof of concept for the combined therapies

within this eight week frame, and maximize the synergistic effect by engaging the same regions as targeted by the tDCS (figures 1 and 2). Also, cognitive training targeted to specific domain of impairment vs. broad spectrum may have utility in MS to ultimately tailor to a patient's specific needs[37].

Training will be comprised of traditional training tasks that have been demonstrated to lead to benefit, both with and without adjunctive tDCS (dual n-back, auditory and visual span, simple arithmetic, and match-to sample [1, 38-46]). Designed and customized for research, we will use classic working exercises through a platform designed by Lumos Labs[47], due to our experience with their high level graphics, high user engagement[6], ease of administration, and ease of data extraction. Based on our experience using this with MS participants, we have found these games to be the best-designed with the highest compliance rates (e.g., reaching 80% or more of target playing time in a sample of 10 pilot participants[6]).

We have developed a telemedicine tDCS protocol that will facilitate recruitment, increase compliance, and enable designs with multiple sessions to evaluate benefits of a cumulative effect. tDCS urgently requires further study to fully leverage this treatment modality for maximal clinical benefit. Repetitive sessions are necessary to produce cumulative effects as shown in neurophysiology studies and clinical trials for neuropsychiatric disorders and rehabilitation [25, 48-50]. For the treatment of depression, a clinical application that has received extensive study, some patients have required 20 to 30 sessions or more for optimal improvement [28, 51-53].

We believe that studies of tDCS have been limited by sample size and number of treatment sessions due to the barrier of access for many patients to participate in studies requiring multiple consecutive clinic visits for treatment. Daily travel to a treatment facility is a real-world limitation because it is not feasible for those with a full work and family schedule (requiring time taken from meeting these other obligations), and/or limited mobility and/or restricted transportation options (which can be especially burdensome for caregivers). *To study multiple applications of tDCS, participants must have the option to be able to access these treatments from home.*

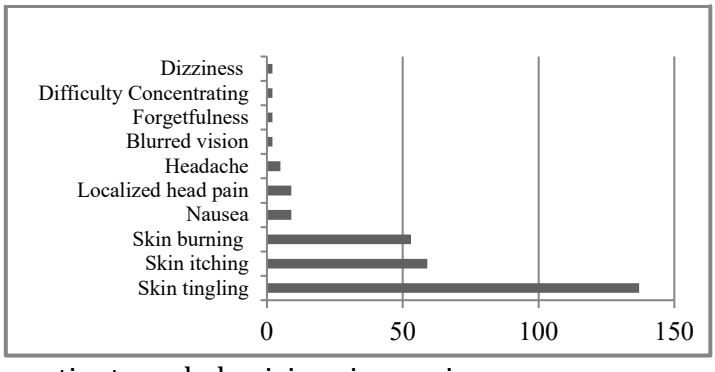
To address this need, we have developed a remotely-supervised telemedicine protocol to provide access to tDCS treatment to participants in their homes (Remotely Supervised tDCS or RS-tDCS). Our protocol was developed following our group's extensive experience with a remotely-supervised cognitive remediation program [6], and meets collaborative guidelines and standards that we established working with a diverse group of tDCS clinical investigators [54]. As detailed below, our protocol is opposed to self-directed home use, where a patient is given a device without parameters and real-time supervision, which is not advisable due to both safety concerns as well as problems with uniformity and reproducibility of results. Instead, we maintain clinical trial standards for safety and consistency with a specially-designed tDCS device (that "unlocks" one "dose" per code, controlled by a study technician) with extensive checkpoints and built-in safety features for study using remote supervision through a telemedicine videoconferencing platform (VSee).

Feasibility and safety study for the RS-tDCS protocol Consistent with the demonstrated safety and tolerability across hundreds of clinical trials in tDCS [17, 18] , including a total of eight published trials in MS [20, 22, 25, 26], we found very high tolerability in our feasibility study. In approximately one year, and at two institutions,
We have administered 1000 RS-tDCS sessions, including >700 active sessions in n=62MS participants (approaching the combined published experience of tDCS in MS) and n=12 PD participants. Participants have ranged in age from 19 to 74 years and included individuals with a range of disability from mild to severe or wheelchair dependent disability. No adverse effects or

side effects of severe intensity have been reported in any session, and no session has been discontinued. As seen in **Figure 1**, the most common adverse event reported was skin tingling, and this did not exceed an intensity of "moderate."

We have experienced rapid enrollment, limited only by device and staff availability (53 patients on a waitlist over a three-month period). Compliance has been near-universal and all but three participants (95%) completed study sessions (this study discontinuation was due to personal family events unrelated to tDCS or the study). Further, the majority of participants have reported benefit from tDCS and requested to continue past study participation.

Figure 1: Tolerability across >500 active RS-tDCS sessions



From our high rate of tolerability and great interest from patients and physicians in previous studies, we believe expanding our tDCS protocol to open-label trials for general neurological disease offers the potential for direct clinical benefit.

While we have focused the development of our methods in participants with MS and PD, both cognitive remediation along and in combination tDCS treat the symptom of cognitive impairment as it occurs across a wide range of disorders [23, 25, 43].

III. SPECIFIC AIM

Specific Aim: To test the feasibility and tolerability of augmenting cognitive remediation with tDCS. Once referred to receive cognitive remediation, eligible and interested participants (n=100) will receive up to sixty daily 20-minute sessions of active (up to 4.0 mA) tDCS paired with their completion of the cognitive tasks.
We will determine the dosing parameters for optimal treatment across individual participants, depending on the nature and severity of baseline deficits.
The *primary outcome* for feasibility will be the number of participants completing at least 80% of the targeted number of sessions. Secondary outcomes will be analysis of tolerability and participant-reported side effects.

IV. DESCRIPTION OF THE PROTOCOL

A baseline neurological and neuropsychological assessment will be completed in-clinic before patients begin the cognitive remediation program. Pending the results of these assessments, participants who are eligible for cognitive remediation will be referred to the study. For the 60 cognitive remediation sessions, eligible participants will receive 20 minutes of active tDCS stimulation (up to 4.0 mA, montage to be determined based on clinician input) while they complete the cognitive training tasks. Once the participant has completed his/her 60 sessions a follow-up neuropsychological assessment will be completed.

V. SUBJECT SELECTION

Characteristics of the Research Population

We will enroll a total of n=100 adults (ages 18 and over) with a clinician referral to receive cognitive mediation.

Eligibility Criteria

While expected to have cognitive impairment, based on our extensive experience with cognitive remediation studies and tDCS, we will exclude participants with an estimated premorbid level of cognitive functioning in the below average range (estimated by reading recognition on the Wide Range Achievement Test-4th Edition or WRAT-4 [55]) and a Symbol Digit Modalities Test or SDMT [56] score ≥3.0 SD published age-referenced normative means will be excluded to ensure basic cognitive capacity to participate. In the case of the potential participant having either speech, motor or vision impairment secondary to their condition that will limit the completion of the SDMT and WRAT-4 screening measures, we will use the following substitution:

- For the WRAT-4 word reading test, using reading recognition and vocabulary as an estimate of general and premorbid intellectual functioning, we will use the following alternate tests: Peabody Picture Vocabulary Test- 4th edition (PPVT-4) that is a nonverbal alternative or the Wechsler Abbreviated Scale of Intelligence-2nd Edition (WASI-2) expressive vocabulary test (that does not require vision).

As with the WRAT-4, the cutoff for these substitute tests will remain less than 1 SD below age normative means.

- For the SDMT measure, used to estimate information processing and degree of cognitive impairment, we will substitute with the following alternate tests: Written condition of the SDMT for a nonverbal alternative or the Wechsler Adult Intelligence Scale-fourth edition (WASI-IV) Digit Span (that does not require vision) combined with either the a) WASI-2 Matrix Reasoning subtest (nonverbal reasoning that does not require motor function) or b) WASI-2 Similarities subtest (verbal reasoning that does not require motor functioning).

As with the SDMT, for these measures, we will continue to use the cutoff of less than -3 SD below age normative means.

Exclusion criteria will include any health condition contraindicated with the use of a tDCS device (including skin disorders, head trauma or medical device in the head or neck).

Inclusion Criteria	Exclusion Criteria

• At least 18 years of age • Clinician Referral for cognitive remediation. • Have undergone a neurological examination and neuropsychological examination as part of standard of care. • Has access to internet service at home compatible with the study laptop (Wi-Fi or ethernet cable) • Able to commit to the designated period of study training sessions with baseline and follow-up visits. • Able to understand the informed consent process and provide consent to participate in the study	• Visual, auditory and motor deficits that would prevent full ability to understand study instructions or operate the tDCS device or study laptop, as judged by treating clinician or study staff • Primary, uncontrolled psychiatric disorder that would influence ability to participate • Poorly controlled epilepsy • Medical device implanted in the head (such as Deep Brain Stimulator) or in the neck (such as a Vagus Nerve Stimulator) • Any skin disorder/sensitive skin (e.g., eczema, severe rashes), blisters, open wounds, burn including sunburns, cuts or irritation, or other skin defects which compromise the integrity of the skin at or near stimulation locations (where electrodes are placed) • Treatment for a communicable skin disorder currently or over the past 12 months • Other serious uncontrolled medical condition (e.g., cancer or acute myocardial infarction) • Wide Range Achievement Test-4th Edition (WRAT-4) Reading Recognition score <85* • Symbol Digit Modalities Test (SDMT) ≥3.0 SD below published norms* • Learned English language after 12 years of age • Pregnant or breastfeeding *In the case of the potential participant having either speech, motor or vision impairment secondary to their condition that will limit the completion of the SDMT and WRAT-4 screening measures the substitutions as mentioned above will be used.

Gender and Minority Inclusion of Subjects

Subjects will be enrolled into the study regardless of gender or minority status.

Vulnerable Subjects

Some participants referred may have cognitive impairment or other debilitating symptoms and could be considered a vulnerable population; however, those who lack capacity to consent will not be enrolled in this study. For all participants, we will confirm capacity to consent with their referring clinician before the visit. We will also screen those with estimated overall cognitive impairment and reading ability by administering a reading measure Wide Range Achievement Test 4 (WRAT-4). It will be clearly explained and written for all potential participants that the study is entirely optional and there will be no negative consequences if their decision is not to participate.

VI. METHODS AND PROCEDURES

a) Study Design: Participants will be referred by their treating physician to receive cognitive remediation. Following this referral, participants will be screened for general eligibility before completing a baseline neurological and neuropsychological assessment to determine eligibility for the study. Subjects will receive the type of neuropsychological evaluation for which they were originally referred. Once participants are found eligible they will complete up to 60 sessions of cognitive remediation while receiving 20 minutes of up to 4.0 mA tDCS using a montage based on presenting cognitive deficits. Subjects will not be required to complete additional sessions for research. The first session is completed at baseline with the option for the remaining sessions to be completed at home using the RS-tDCS protocol. If for some reason participants are not able to complete the training from their home, they will have the option to receive treatment at clinic.

Screening:

Participants will primarily be recruited from the NYU Langone Medical Center. Once a participant is deemed generally eligible following their neurological and neuropsychological evaluations, the individual will be scheduled for a visit at NYU to review and sign consent and complete screening procedures. For those interested in study participation, once eligibility is confirmed by the study PI, their cognitive remediation and tDCS training will be scheduled.

Baseline Visit:

***Note PI assessment for eligibility may occur either before or at the baseline visit**

Prior to tDCS training, the tests and evaluations detailed in Table 2 will be administered.

tDCS aptitude screen and tolerability test:

- **tDCS Aptitude: Participants will first complete an aptitude test to confirm that they have the cognitive and motor skills required for headset placement.**

With instruction of the study technician, participants will be asked to insert the sponges onto the headset and place the electrodes into the sponges. The technician will determine whether or not the participant is qualified to proceed. Participants will not be allowed to proceed if they are not able to correctly either 1) attach sponges to headset or 2) place electrodes into the sponges.

tDCS Tolerability: The study technician will next directly place the headset and then initiate a one-minute test session, with 30 seconds of ramp-up to target, following by 30-second ramp down. The tolerability test will first take place using 2.5 mA stimulation. If the participant tolerates and agrees, 3.0 will be tested; again

if the participant tolerates and agrees, the next increment of 3.5 mA will be tested; as follows, increases will be made to 3.5 and 4.0 mA respectively (note: the option for increase is device-dependent; some current devices have a maximum of 2.5 mA programming). Alternatively, if the participant cannot tolerate 2.5 mA, stimulation will be based on highest amplitude tolerated, following 0.5 mA decrements (with 2.0, 1.5., and 1.0 mA stimulation offered). Once the tolerable dose is established, it will remain constant throughout the study. If the participant cannot tolerate any offered stimulation levels, they are excluded from the study.

- A total of 20 x 20 minute sessions is targeted, with the option for up to 60 x 20 minute sessions to be completed. The minimal goal of 20 sessions completed will continue up to 60 treatment sessions if jointly agreed between the study participant and referring clinician.

Remotely Monitored Study Sessions:

Study Equipment: For the remotely-supervised sessions, participants will be given the specially-designed tDCS device and headset, study laptop computer for secure video monitoring with study technician (must have internet access) and a training video. The Soterix mini-CT is uniquely designed for remotely-supervised delivery and requires a one-time use code provided by the study technician to unlock the device for one stimulation session at a time. The device will not operate without correct headset placement and has a single-button option to abort the session. The device will also automatically abort the session if optimal conditions are not maintained. It reports and records a completion code for each session.

These sessions will be completed from home with remote monitoring by the study technician.

Participants will schedule times during which they are certain they can self-administer the tDCS while they are being remotely monitored by study staff. They will be observed using a secure internet-based video chat program that will be installed in the laptop they will use for the study. To start their session, the participant will connect to study staff via VSee. VSee is a HIPAA compliant teleconferencing software that encrypts data before sending, creating a secure connection between two computers.

They will put on the tDCS headgear while being monitored, and tell study staff if the device feedback indicates that the electrodes are acceptably placed. The participant will then receive the activation code from the tDCS device. If the study staff observes the participant making any errors that may cause the latter discomfort they can intervene with instructions for correction.

Montage:

We currently use the dorsolateral prefrontal cortex (DLPFC; left anodal) montage. We will expand to the other commonly-used tDCS montages to be matched depending on referring clinician's input. Most participants will receive the montage with the standard DLFPC cortex (left anodal) montage. However, in some cases, with clinician input a different montage may be used for current delivery[18, 57]. For instance, if there are primary visuomotor integration problems, the M1-S0 montage may be used instead. Or, if there are primary visual processing difficulties, an occipital lobe montage may be used. All montages will follow the standard placement systems[58] as available through the device company Soterix, and with no safety or tolerability issues noted between differing montages[18].

Safety notes:

- The tDCS device can only operate if: 1) the headset is correctly placed for adequate connection, and 2) the study technician provides a session code that unlocks the device for a one-time only 20 minute period of use.

- If the device loses adequate contact for any reason, the device will automatically discontinue the session. The session can only be reestablished if another unlock code is provided by the study technician.
- If the participant wishes to discontinue the session at any time, they will be instructed to press the "abort" key which ramps down the current within 30 seconds to allow for headset removal.

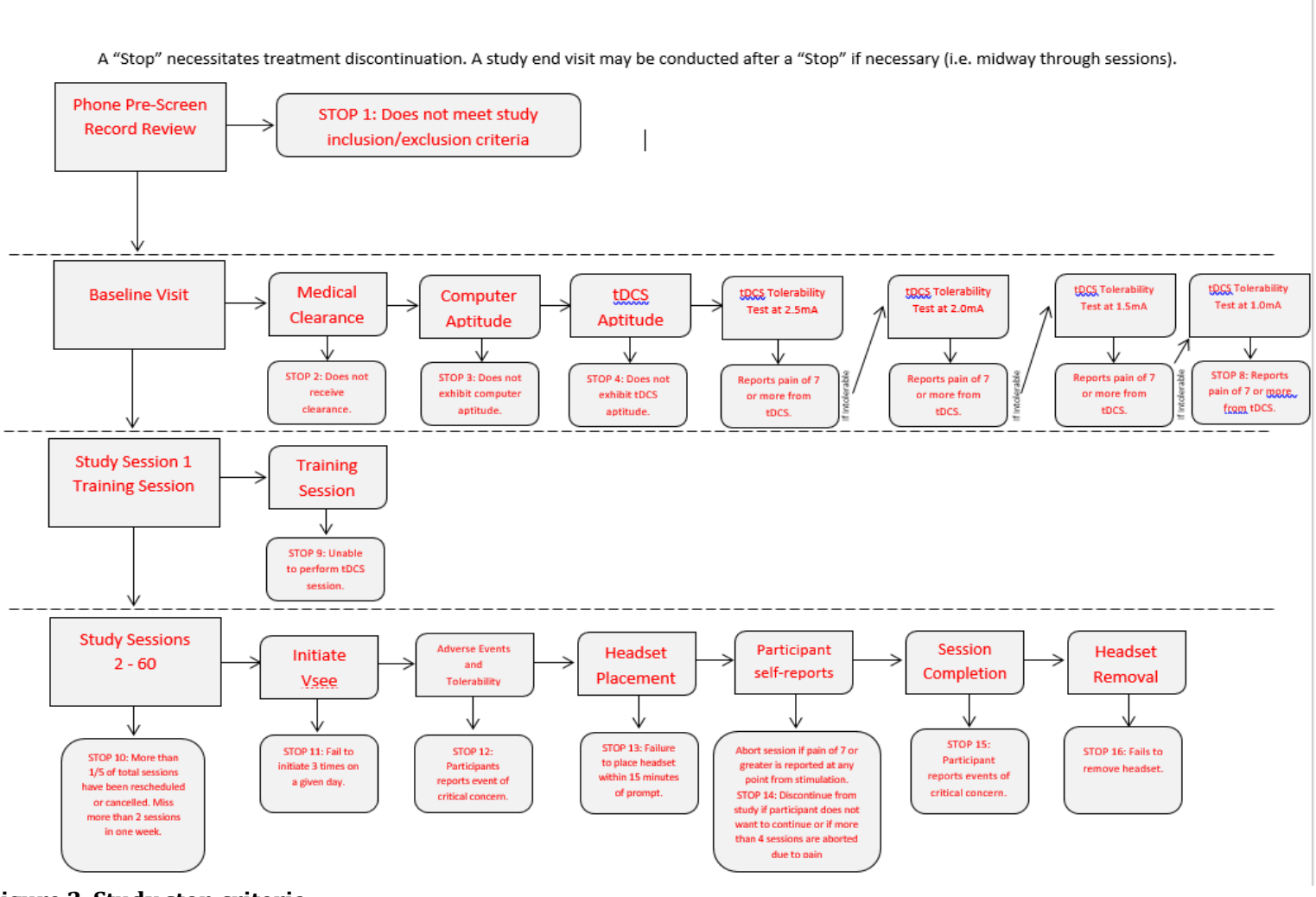


Figure 2. Study stop criteria

Study End Visit:

Within three days of their last session (including same day), participants will have their final study end visit in clinic. The tests and evaluations administered at baseline will be given to the participant again (Table 1). The equipment that had been provided to the participant for this study will be returned on this visit.

Outcome Measures: Before and after each session, participants will complete brief measures to monitor for any stimulation-related events. Brief measures will also be given to monitor any therapeutic or behavioral effect of the tDCS stimulation. To further inform tolerability of stimulation sessions, a pain scale will be administered before, during, and after each session. Participants will also complete baseline and study-end inventories of cognitive and behavioral

measures to help guide power estimates for the future trials. A summary of outcome measures can be found in Table 2.

All remotely-supervised sessions will be completed while connected to a video session with the study technician. The protocol is designed to have a decision-tree series of checkpoints that must be met in order to proceed at each step (Figure 2). These checkpoints address compliance (attendance, ability to complete the procedures as instructed, following the study guidelines) and tolerability (at any time, if any predefined events are reported, or if pain crosses a threshold the participant will be discontinued).

Table 2. Study Outcome Measures

Test	Screening	Baseline	Daily Study Sessions	Study End/Follow-up Visit	Post Study Survey (at least 1 month after study end)
Medical Clearance	x	x			
Wide Range Achievement Test (WRAT-4)	x				
Symbol Digit Modalities Test (SDMT)	x	x		x	
tDCS Aptitude Test		x			
tDCS Tolerance Test (4.0, 3.5, 3.0. 2.5, 2.0, or , 1.5, or 1.0 mA)		x			
PROMIS Measure of Fatigue, Mood and Health-Related Quality of Life		x		x	x
Cogstate		x*		x*	
Test of Everyday Cognitive Ability		x*		x*	
King Devick		x*		x*	
Hand grip and pinch strengths		x*		x*	
Symptom Specific Measures (Cognitive and behavioral)		x	x	x	
Cognitive Linguistic		x*		x*	

Quick Test, The Communicative effectiveness Index, Western Aphasia Battery Part 2					
Positive and Negative Affect Scale (PANAS)		x	x	x	x
Visual analog scale for pain (pre-, mid- and post-session)		x	x		
Tolerability questionnaire administered by study staff (pre- and post-session)		x	x		
Safety and tolerability questionnaire - self-report (pre- and post-session)		x	x		
Score for Computerized cognitive games (daily)			x		
Participant evaluation of study procedures and report of their experience				x	x
Count of successful tDCS sessions (confirmation code by session days)				x	

*- Optional measure

VII. STUDY LOCATION

Participants screening, baseline and study end visits will be completed at the NYU Langone MS Comprehensive Care Center, 240 East 38th Street, 18th Floor, NY NY 10016, or the satellite location for the

MS Center: NYU Langone Huntington Medical Center, 789 Park Ave, Huntington, NY 11743. For participants with limited mobility, visits can be completed from the participant's home.

Additionally, 222 East 41st Street, 10th Floor is a third available study location.

VIII. DATA ANALYSES AND DATA MONITORING

Database and Patient Information

Data will be entered in the HIPAA- compliant NYU REDCap database designed specifically for this study. An anonymous database number will be assigned to each participant and will be used for both the Data Entry Sheet and the Patient Follow-up Sheets. The original front sheet, which includes the patient name and ID number, will be stored separately in a locked filing cabinet in a locked office. Access to this data will be restricted to study personnel only. Research data will be entered online through the secure NYU database software REDCap and source documents will be kept in a locked filing cabinet in a locked office. Patient clinical data will be entered directly into the Patient Registry (on-line entry). Participant data will be coded by the assigned ID and identifying information will not be presented or published to maintain participant privacy and confidentiality.

Additional Quality Assurance Measures

- Development of standard protocols to perform all data collection and follow-up activities.
- Use of standardized forms.
- Uniform criteria for patient recruitment.
- Standardized data processing.
- Regular communications between study staff and study investigators to resolve questions.
- Performance monitoring of data collection and data processing activities, as well as preparation of periodic reports and analyses on performance monitoring.
- Monthly monitoring of recruitment statistics.

Data and Safety Monitoring Plan

We will utilize operating procedures for reviewing patient safety data and source data generated from this study. This will include weekly meetings between the PI, the Co-I (Dr. Lauren Krupp), and study coordinators. At these meetings, the entire research team will review the clinical ratings, assessments, clinical course, and medical records for each subject. Consideration of dropping any patient from the study for any reason will be discussed. If after the completion of the first 20 subjects the compliance is significantly low, the study will be put on hold and reviewed. Based on the extensive body of literature using tDCS across a range of conditions, and our initial participants studied to date (completed at Stony Brook Medicine), we have had >94% compliance in the active condition. Due to our success with compliance in previous studies, we do not expect severe compliance issues. Still, we are prepared to deal with compliance problems, if there is significantly poor compliance, we will be able to identify reasons including tolerability as well as symptom experiences. Tolerability is measured before, during and after each session and all participants will be monitored for all sessions. Safety is carefully addressed in our protocol with a series of stop criteria and clearly defined action items.

Specific attention will be given to data quality and timeliness, HIPAA-complaint, safe storage of data, and data backup of electronic source data. Attention will also be given to participant recruitment, accrual and retention, participant risk versus benefit, adverse events, and other factors that can affect study outcome, including scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.

Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Inter current illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Definition of Serious Adverse Events (SAE)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

We will submit study data safety monitoring reports to the IRB after 10 participants are enrolled, and follow with reports for each further increment of 10 active enrollees.

Statistical Analyses

Analyses will be completed with IBM SPSS v. 23. Means, medians, standard deviations (SD) will be compared between subgroups on the measures using conventional cut-off points for each of the symptoms will be compared. Our sample size (n=100) was determined by a power analysis indicating over 90%in determination of feasibility and tolerability.

Specific Aim 1 will be tested by assessing the compliance (<80% sessions completed) of study participants within groups established by disease, age, EDSS scores etc. We will also assess any reported side effects of active tDCS treatment to determine general tolerability
Secondary outcomes will be used to compare the groups in change in performance on the additional measures listed in Table 2. In addition, performance on the WM CT will be analyzed across training sessions, including time to advance to a new level and overall levels achieved. Similar analysis as what have been planned for the primary outcome will be performed for comparing the change in these secondary outcomes between before and after the completed sessions.

Neurological clinical features (age, gender, disease, treatment, disease duration) will be compared by correlational analysis.

IX. SUBJECT RECRUITMENT AND CONSENT/ASSENT

Subject Identification, Recruitment and Consent/Assent

Method of Subject Identification and Recruitment

NYU Langone Medical Center has an extensive recruitment base. Patients who are seen by medical staff at NYU Langone Medical Center, who fit the eligibility criteria, will be referred for the study by the study PI, Co-I, and sub-investigators. If the patient is interested and agrees, then a member of the study staff will contact them. Once a patient is identified, study staff will meet with the patient or call them to provide additional information regarding study participation. After the patient has reviewed the consent form and asked all questions, and provides consent to participate, the patient will be enrolled in the study.

Advertisements

An IRB approved flyer will be posted in local physician offices and waiting rooms and throughout NYU, the surrounding community, and on Long Island. A description of the study will be posted on sites related to neurological disorder.

Process of Consent

All potential participants will complete a screening interview to ensure general eligibility. The study staff member speaking to the subject will provide the subject with an overview of the study and verbally receive their permission, under a waiver of documentation of consent, to complete the general eligibility screening. The pre-screening measures will include reading recognition on the Wide Range Achievement Test-4th Edition or WRAT-4 [55] and a Symbol Digit Modalities Test or SDMT [56]. In the case of the potential participant having either speech, motor or vision impairment secondary to their condition that will limit the completion of the SDMT and WRAT-4 screening measures the substitutions as mentioned above will be used. If a participant is not eligible, they will be considered a screen fail. No additional information will be collected. PHI will be destroyed immediately if a participant is not eligible or does not return to sign written consent/authorization to participate. Only study staff will have access to these records.

Once the participant is generally eligible, the PI, or one of the trained study team members will review the consent form with the subject and explain the purpose of the study, the procedures, as well as risks and benefits. All questions will be addressed before acquiring the participant's signed consent. Subjects must have capacity to consent in order to be enrolled in the study.
Referring clinicians and NYU clinicians doing the medical screening will be responsible for assessing the capacity to consent. An independent assessor will not be utilized. There is a large body of literature indicating no known safety or tolerability risk for use of tDCS. Further, tDCS is currently being studied as an alternative to relatively higher risk treatments (such as medication) in special populations such as pregnant women and developmentally disabled children.

Published studies in MS, including the work in our lab at Stony Brook Medicine, show tDCS to be a tolerable and safe treatment approach. Members of the core physician group and team at the MS Center are Neurology specialists with extensive experience in the assessment of neurology patients, including capacity to consent for numerous clinical drug trials where there is a substantially greater potential risk posed than what are the known risks for tDCS. Therefore, taken together, we do not believe that the use of tDCS represents a situation where an independent party would be needed.

Process to Document Consent in Writing

After review of the consent form and prior to the start of the first session, the PI or one of the trained study staff members will obtain written consent with a signature of the patient on the consent form. All original signed consent forms will be maintained in the study file, separate from the participant data.

Subject Capacity

All participants will be confirmed to have the capacity to provide consent by a member of the core physician group as described above. Further, those participants with estimated premorbid intellectual functioning and/or impaired reading ability (as determined by the WRAT-4 Reading Subtest), and those with severely impaired information processing speed (as determined by the SDMT) will be excluded.

Debriefing Procedures

No information will be purposely withheld from the subjects. A clinical neuropsychologist (PI) and the treatment team will be available to answer any questions concerning the tests and results, and provide initial feedback as warranted, including referral for clinical neuropsychological assessment.

Consent Forms

Participants will receive a NYU consent form to review and sign prior to participating in the study.

Documentation of Consent

The PI is responsible for ensuring that valid consent is obtained and documented for all subjects. An enrollment log will be maintained and consent forms will be kept in secure location separate from the participant's data.

Costs to the Subject

If subjects choose to participate, the cognitive remediation sessions will be provided to them without cost for that care. The MS Center medical secretary who oversees billing authorization for clinical neuropsychological service will perform insurance authorizations. Following procedures for clinic appointments, prior authorization will be obtained and the participant will be informed of any potential costs prior to scheduling and enrollment. Both the cognitive remediation and tDCS will be covered by the research team, further no additional sessions will be required for research purposes. If subjects have been referred for other clinical services in addition to cognitive remediation or if the clinical review of their case indicates that other treatments would be appropriate, these treatments would be provided at a cost to subjects based upon their insurance coverage. Subjects will be informed of their payment responsibilities before they are enrolled in the study during the pre-screening phone conversation (see Section IX, Process of Consent).

Payments to the Subject

Subjects will not be compensated for their participation in the study.

Risk to Participants

As described above, tDCS poses low risks to participants and our protocol is well-tolerated [18]. To our knowledge, hundreds of tDCS studies in the US have all been designated Non-Significant-Risk (NSR) the lowest risk level (devices that are not: intended as an implant with potential for serious risk to health, safety, or welfare of subject; purported or represented to be for use in supporting or sustaining human life with a potential for serious risks; for use of substantial importance in diagnosing curing, mitigating, treating disease or otherwise preventing impairment of human health with potential for significant risk; otherwise presents significant risk to the health, safety, or welfare of a subject). For these reasons, the Soterix Mini CT, as used in this study, also qualifies as a NSR device. While tDCS remains an investigational technique (simply because no company has applied to the FDA for approval to market tDCS for any given indication), tDCS is a broadly reproduced and tested techniques that is considered effective in modulating brain excitability in a manner that may support learning and with adverse events (different than sham) limited to tingling, itching, and redness that dispel after stimulation stops. In a prior study of use in a vulnerable population (developmentally disabled children), the FDA issued a NSR for tDCS device (see attached letter). The letter provided as an example of the FDA's designation of tDCS devices as having abbreviated-IDE. Because of its prior designation of tDCS devices as abbreviated-IDE, trials do not typically seek further declaration. In the letter provided, Dr. Wasserman specifically sought FDA review of the trial due to the use of tDCS in a vulnerable population (developmentally disabled children). To date, hundreds of trials have been designated as non-significant-risk by IRB review which provides its abbreviated IDE status. Results of completed trials, including our own work in MS using this protocol, have supported the risk designation provided by IRBs. The Stony Brook Medicine IRB confirmed the NSR and abbreviated IDE status of tDCS for our study.

and others at the institution. We have learned that the NYU IRB has also confirmed tDCS devices (including those manufactured by Soterix) as having an abbreviated-IDE for current ongoing studies at this institution for other indications.

The safety of this technique has been addressed and tested by multiple researchers (Fregni, et. al. [59]; Nitsche, et al. [60]; Priori, et al. [15]) who have concluded that tDCS, as applied in a manner similar to our proposed protocol, induces only temporary mood, cognitive / motor effects, and no negative side effects.. For example, researchers at the National Institute of Neurological Disorders and Stroke (NINDS), Iyer et al. [17] conducted a safety study on tDCS, investigating 20-minute sessions of 1 mA and 2 mA current stimulation with healthy controls (n=103). No negative effects were identified. Nitsche and colleagues found no measurable structural changes in brain tissue due to tDCS [61]. In a meta-analysis of over 200 tDCS studies conducted from 1998 to 2010, 56% of studies mentioned adverse events, which were generally minor. The most commonly reported side effects included itching, tingling, headache, burning sensation and discomfort limited to the scalp site where the tDCS electrodes were applied. To date, there have been no reports of seizures induced by tDCS[14]. Importantly this is the case in normal volunteers, but also in different populations of patients, including patients with disorders where there might be an increased risk of seizures (e.g. Alzheimer's disease, recent stroke, epilepsy). A study from NYU on the use of tDCS in patients with epilepsy [62] encountered no increase in complications of tDCS in the patients as compared with controls. Specifically, there were no instances of seizures induced by tDCS.

Participants in all groups may find the questionnaires time consuming and potentially bothersome. Neuropsychological testing and the computer training sessions may, in some individuals, be stressful or anxiety producing. There is a small risk of loss of confidentiality. Participants will be assigned a study ID and their name will not be used on any of the information collected. The program used for brain training games will not collect any personally identifiable information. The results of these data collected may be used for publication but will not include the participants' names. Hardcopies of the data files will be kept in secure, locked files and data will be entered in a secure, NYU approved database.

Benefits to Participants

Participants may have some benefit from this study. The therapeutic techniques used may, on their own, be of benefit to the participant. Cognitive remediation can have an increase in cognitive functioning through the use of the tDCS device. We hope the knowledge gained from this study will help others in the future.

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