A pilot study of remotely-delivered transcranial direct current stimulation (tDCS) in adults with multiple sclerosis (MS) (S15-01189)

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I. PURPOSE OF PROTOCOL

The proposed study will test the tolerability and preliminary efficacy of transcranial direct current stimulation (tDCS) combined with a cognitive training program, remotely-delivered using a telemedicine protocol in n=85 adults with multiple sclerosis (MS) and in n=30 adults with Parkinson's Disease. Overall, the enrollment goal for this study shall be n=115. The objective of this study is to establish a study protocol to use in clinical trials to evaluate the efficacy of tDCS to ameliorate two of the most debilitating symptoms of MS that remain without effective treatment: cognitive impairment and fatigue.
We developed the protocol to be used for this study at our former institution, Stony Brook Medicine, and have published the results[1]. As described below, it has been tested in n=20 adults with MS with over 192 active sessions. The tDCS administered in our protocol has been very well-tolerated (all sessions successfully completed, no side effects reported to be more than moderate level).

II. BACKGROUND

MS is a common disorder associated with major costs. MS is characterized by demyelination, immune-mediated inflammation, and neurodegeneration within the central nervous system[2, 3]. The most common subtype is relapsing-remitting and over half of these individuals transition to a progressive course; the remainder have a progressive course from the onset[4]. MS is the most common progressive neurologic disorder in adults of working-age[5]. It is estimated to affect more than 2.3 million people worldwide including over 400,000 individuals in the US costing up to ~$52,000 per patient per year [5, 6].

tDCS is a novel, safe, well-tolerated and low-cost treatment approach that strongly warrants investigation in MS. The application of tDCS is a relatively recent therapeutic development that utilizes low amplitude direct currents to induce changes in cortical excitability[7, 8]. tDCS is expected to produce neuronal polarization of less than one mV [9]. tDCS produces relatively diffuse current flow, as demonstrated by imaging studies and computational models[10, 11]. 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[12].

tDCS produces current intensities in the brain orders of magnitude below other stimulation techniques such as transcranial magnetic stimulation (TMS) or electroconvulsive therapy (ECT) [13]; tDCS has none of the significant side-effects reported with these much 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 [8, 14].

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[15, 16]). With an extensive record of safety and tolerability, the most common side effects are specific to the

electrode site and include itching, tingling, and burning[17]. 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[18,8, 19, 20,21, 22] and may be preferred to drug treatment in special populations (such as pregnant women[18]) due to its safety advantages.

tDCS is considered especially promising for symptomatic treatment in MS both for its tolerability, deployability (based on our innovative remotely-supervised approach), and presumed mechanism of action. While there is emerging study the cellular mechanisms of tDCS[23], what is established is that sustained (minutes) of tDCS can produce lasting changes in brain excitability[24] and that these changes are plastic and cumulative with repeated sessions [25]. One of the largest and more reproducible effects in healthy volunteers is enhanced vigilance with an increased ability to engage selective attention[23, 26-28], a finding which may indirectly underpin the cognitive benefits of tDCS[29, 30]. In clinical populations, one of the most replicated measures is elevated mood and has been considered an effective treatment for depression.

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 in MS. Repetitive sessions are necessary to produce cumulative effects as shown in neurophysiology studies and clinical trials for neuropsychiatric disorders and rehabilitation[8, 31-33]. 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 [33,20, 29, 30, 34].

We believe that studies of tDCS in MS have been limited by sample size and number of treatment sessions due to the barrier of access for most MS 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), or limited mobility and/or restricted transportation options (which can be especially burdensome for caregivers). For example, all but one study of tDCS in MS to date (treating symptoms of pain, fatigue, sensory and motor functioning [31, 35-40]) has included more than five sessions, and none have enrolled more than 31 participants (and, in this largest sample size, participants only completed one tDCS session[31]*). To study multiple applications of tDCS in MS, participants must be able to access these treatments from home.*

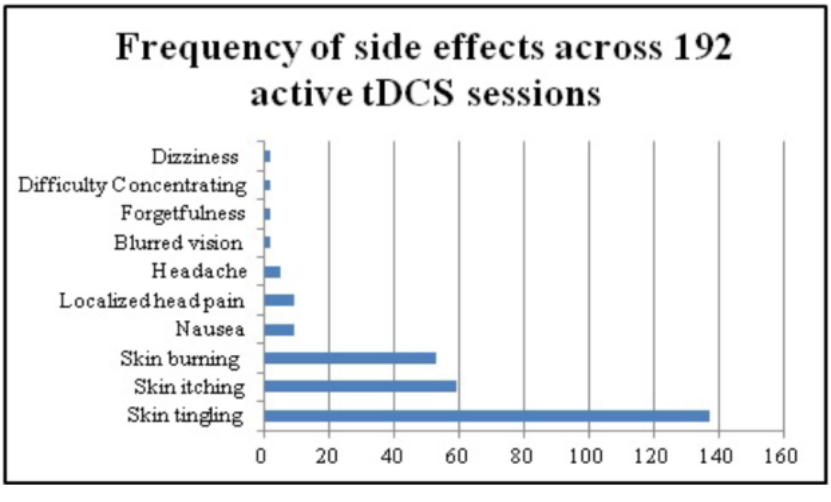
To address this need, we have developed a remotely-supervised telemedicine protocol to provide access to tDCS treatment to participants in their homes. Our protocol was developed following our group's extensive experience with a remotely-supervised cognitive remediation program [41], and meets collaborative guidelines and standards that we established working with a diverse group of tDCS clinical investigators[42]. 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.

Feasibility and safety study for our telemedicine tDCS protocol Consistent with the demonstrated safety and tolerability across hundreds of clinical trials in tDCS[58,59], including a total of eight published trials in MS[43,35, 37, 38, 44], we found very high tolerability in our feasibility study. In less than five months

we administered 192 active tDCS sessions in n=20 MS patients receiving 10 open-label sessions over two weeks (approaching the combined published experience of tDCS in MS fatigue). Participants have ranged in age from 30 to 69 years and included individuals with all subtypes (n=6 relapsing remitting, n=12 secondary progressive, n=2 primary progressive), and a range of disability from mild to severe or wheelchair dependent disability (EDSS scores of 1.0 to 8.0). 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."

Due to both the novelty of tDCS and the option to participate remotely, we have met great interest in our MS patient community with 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 one participant (95%) completed at least 8 of the 10 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 the study's 10 sessions.

Figure 1: Frequency of side effects reported across 192 tDCS sessions with remotely-supervised protocol



III. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

The objective of this study is to establish a study protocol to use in clinical trials to evaluate the efficacy of tDCS to ameliorate two of the most debilitating symptoms of MS that remain without effective treatment: cognitive impairment and fatigue.

Cognitive impairment:

Cognitive impairment occurs frequently in MS and is without an effective treatment option: Cognitive impairment occurs in up to 70% of all patients[45-47] and, in this younger adult population, is a major cause of disability leading to unemployment, social isolation, and increasing dependence on caregivers[48, 49]. The most common deficits are in the area of working memory (WM), measured by tests of information processing, attention, and new learning[50-52]. Impairment can occur independently from other disease features[47] and is linked to cerebral atrophy, and, in particular, regional grey matter volume loss[53]. Unfortunately, medications have not been effective[47, 54, 55]. Disease-modifying medication possibly slows the progression of deficits, but does not improve functioning[55-59]. Symptomatic medications such as the

cholinesterase inhibitor donepezil (trials completed at our center)[60-62] and L-amphetamine are not effective as standard treatment[63, 64] and can include safety concerns (e.g., potential for abuse[65]).
•Neural plasticity-based computerized cognitive training (CT) programs are promising: There has been limited study of CT in MS. Traditional approaches (e.g., clinician-delivered compensatory strategies and drill-and-practice training) are costly and difficult to uniformly implement, with inconsistent benefit[66-69]. Recent technological advances have led to computer-based CT approaches[70-73]. Rather than focusing on compensation, intensive repetitive targeted exercise may actually improve cognitive ability at the processing level, possibly through mechanisms of neural plasticity[71-76]. This *plasticity-based* approach aims to drive change with exercise components including trials that are rapidly adapted to the individual user in real-time to maintain a consistent level of challenge[71, 73]. Initial studies in MS have linked cognitive reorganization with training[77, 78].

We have completed two controlled trials in MS demonstrating the superiority of this type of CT compared to ordinary computer games. Our group has developed a protocol to allow participants to access CT from home, targeting 60 sessions over 12 weeks [41]. The *remote access has resulted in rapid enrollment of >160 patients* in two years; in comparison, in the largest published CT trial in MS, an outpatient memory training program with10 sessions in five weeks, required *>7 years* to enroll n=86 participants[68]. Using our protocol we have found very high compliance, with no loss of study equipment, weekly participant phone interviews, and all but two completing the program through the study end visit. These results emphasize the tremendous unmet treatment need for people living with MS, and have led to the established procedures to be used in this study to deliver remotely-supervised cognitive remediation.

•tDCS can increase the benefit of CT: While many questions remain, pairing tDCS with CT has increased learning and performance particularly in tasks depending on WM[27-30, 79-81]. Preliminary data from our recently-completed randomized double-blind active-placebo controlled trials show that CT leads to leads to greater gains in a neuropsychological testing composite z score when compared to playing ordinary computer games (n=135, program by Posit Science[82], p=0.02, report in preparation; and n=20, program by Lumos Lab, 0.46 ± 0.59 improvement vs.-0.14 ± 0.48 decline, $p = 0.02$ [41]). However, the difference in average improvement of the composite z-score is relatively modest, z-score 0.20±0.36 vs. 0.05±0.31, p=0.02, Cohen's d =0.43. The proposed research will take the first step towards determining whether the benefit of CT can ultimately be improved when combined with tDCS.

Fatigue:
Fatigue is the most frequent debilitating symptom of MS and remains without an effective treatment: 75% or more of patients report it is among their most disabling MS problem[83, 84], and 55% indicate it to be the worst[85, 86]. Defined by the subjective sense of overwhelming tiredness and exhaustion, there are serious adverse health care consequences linked to fatigue in general, and MS fatigue in particular. Fatigued MS patients leave the work force early, have increased health care utilization, and are at risk for depression[87]. However, despite careful description (initially with the Fatigue Severity Scale or FSS, developed by study Co-I Dr. Lauren Krupp), the etiology of MS fatigue remains poorly understood[88]. MS fatigue is neither consistently linked to disease severity as measured by the Expanded Disability Status Scale or EDSS[89] nor disease duration[90], although it is generally found to be worse with individuals with the secondary progressive subtype[83, 90-92]. Fatigue is distinct from sleepiness and fails to improve with adequate sleep[93]. Multiple factors contribute to fatigue, including CNS demyelination and axonal loss[94], immunological changes, MS-related problems (trigeminal neuralgia, spasms), psychological and chronic illness factors (depression, pain, poor sleep), and medications[95, 96].

A wide variety of therapies have been attempted for fatigue in MS but there remains no accepted or standardized treatment[88]. Fatigue may improve with disease modifying therapy but there is no evidence of consistent benefit[97-99]. No symptomatic medication, including large trials of modafinil[100], amantadine and pemoline [101], has been found to be reliably effective[86, 102, 103]. Behaviorally-based management programs (e.g. cognitive behavioral therapy, mindfulness-based interventions), exercise programs[103] and comprehensive strategies to manage MS fatigue directly[104] have also been studied. While these treatment efforts have had somewhat more success than medications, they are costly in terms of clinician and patient time, usually require weekly or more frequent clinic visits for therapy, and are not widely available. Overall, fatigue in MS has remained frustratingly treatment-resistant. A consistently effective, reliable and accessible fatigue treatment option is greatly needed.

Of the eight published trials of tDCS to date, three have directly targeted fatigue[35, 37, 38]. As shown in **Table 1**, all three have used sham-controlled crossover designs, and found significant improvement in fatigue following active treatment in either the full group or subset analyses[35, 37, 38]. Each of the three studies varied in their montage with similar results.

Table 1. tDCS studies of fatigue in MS to date, including our feasibility study and proposed study

Author (Year)	Sample n	Design	#Sessions, Treatment Montage
Ferrucci et al. (2014) [38]	**25**	Sham-controlled crossover	5 sessions x 1.5 mA motor cortex x 15 minutes
Saiote et al. (2014)[37]	13	Sham-controlled crossover	5 sessions x 1.0 mA DLPC x 20 minutes
Tecchio et al. (2014)[35]	**10**	Sham-controlled crossover	5 sessions x 1.5 mA x 15 minutes; sensorimotor cortex
Protocol feasibility study	**17**	**Open-label (remote protocol)**	**10 sessions x 1.5 mA DLPFC x 20 minutes**

Two of the three studies included analyses to link to the mechanism of benefit, with unclear results. Saiote et al.[37] included MRI and found a correlation between lesion load in left frontal cortex and reduced fatigue following tDCS treatment. In a follow-up second analyses, Tecchio et al.[35] found tDCS treatment was more effective against MS fatigue when the electrode was focused on the bilateral whole body somatosensory area (but changes in S1 and M1 excitability did not correspond to treatment benefit).

IV. SPECIFIC AIMS

Specific Aim 1: To test the feasibility of a randomized, controlled remotely-supervised tDCS clinical trial protocol developed specifically for use in MS. Participants (n=85) will be randomly assigned to receive 40 x 20-minute sessions of either active (up to 2.5 mA) paired with cognitive remediation, to two separate control conditions. The first is an active tDCS condition paired with non-adaptive, traditional puzzle and board games and will act as this study's negative control. The second control will act as the study's positive control and will be sham tDCS paired with cognitive remediation. Each study session, regardless of study arm, will be followed by an additional 10 minute computerized training sessions post-stimulation. Each study arm will complete 40 sessions over eight weeks.

The *primary outcome* for feasibility will be the number of participants completing at least 80% or n=32of the targeted 40 sessions. Secondary outcomes will be comparison of tolerability and participant- reported side effects between the two treatment arms.

Specific Aim 2: To test the preliminary efficacy of tDCS to treat fatigue and to enhance outcomes of cognitive training. These data will inform the design of a large, controlled clinical trial.

The *primary outcome* will be comparisons between the active and control conditions on measures of fatigue and cognitive functioning.

V. DESCRIPTION OF THE PROTOCOL

The goal of this pilot study is to establish a structured protocol for safe remotely-supervised delivery of 40 consecutive tDCS sessions (active and control conditions) to be used in a randomized, controlled double-blind clinical studies in participants with MS.

a) Study Design: Participants will complete a total of 40 sessions across eight weeks: training at baseline with a study technician and then monitoring (through secure online video) by the study technician for the remaining thirty-nine sessions. We will use the most common montage of bilateral dorsolateral prefrontal cortex (DLFPC) placement, with the anodal electrode placed on the left side. This offers ease of reliable electrode placement and wide therapeutic applications. Dose will be up to the target of 2.5 mA with reduction to 2.0, 1.5, or 1.0 mA based on tolerability testing at baseline. At study end, participants in the sham condition will be offered 10 open label active sessions.

b) 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), a detailed reference manual, 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. 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.

c) *Randomization:* Participants will be assigned to each condition in a 1:1:1 Stratified randomization procedure. Participants will be matched according to the degree of cognitive impairment (Symbol Digit Modalities test or SDMT[105] score) and neurologic (motor) impairment (Expanded Disability Status Scale or EDSS[89] score). Participants will be randomized to either the active tDCS condition paired with cognitive remediation or one of the two control conditions. The positive control condition will consist of cognitive remediation paired with sham tDCS and the negative control condition will consist of active tDCS with non-adaptive puzzle and board games using block randomization of permuted block sizes 3 and 6, based on our experience in cognitive remediation trials. SDMT performance will be categorized compared to published age-normative means (>0.99 SD, 1 to 2 SD and 2 to 3 SD below mean) and EDSS score will be categorized as mildly or moderately impaired (0 to 3.0 vs. 3.5 to 8.0).

d)***Outcome Measures:*** Before and after each session, participants will complete brief measures to monitor for any stimulation-related events as well as mood and fatigue. In addition a pain scale will be administered during the session. Participants will also complete baseline and study-end inventories of mood and fatigue and complete a brief battery of cognitive tests including the Brief International Assessment of Cognition in MS or BICAMS[106], to help guide power estimates for the future trials. A summary of outcome measures can be found in Table 2.

Table 2. Study Outcome Measures

Test	Screening	Baseline	Daily Study Sessions (1-20)	Mid-study	Daily Study Sessions (21-40)	Study End (Follow-up)	Online/ Telephone Survey (Study end date + 1 month)
Medical Clearance	X						
Expanded Disability Status Scale	X						
Wide Range Achievement Test (WRAT-4)	X	X				X	
Symbol Digit Modalities Test (SDMT)	X	X		X		X	
Beck Depression Inventory-Fast Screen*		X				X	
tDCS Aptitude Test		X				X	
tDCS Tolerance Test (2.0 mA, will possibility to repeat at 1.5 mA)		X				X	
Multiple Sclerosis Neuropsychological Questionnaire (MSNQ)*		X		X		X	X
PROMIS Measure of Fatigue, Mood and Health-Related Quality of Life*		X		X		X	X
Neuro-Quality of Life*		X		X		X	X
Fatigue Impact Scale*		X		X		X	X
Fatigue Severity Scale*		X		X		X	X
Pittsburgh Fatigability Scale*		X		X		X	
Attention Network Test-Interaction*		X		X		X	
Cogstate Brief Battery*		X		X		X	
ERTSLab Processing Battery*		X		X		X	
Controlled Oral Word Association*		X		X		X	
Rey Auditory Verbal Learning Test*		X		X		X	X (delayed recall only)
Brief Visuospatial Memory Test- Revised*		X		X		X	
King Devick Test*		X		X		X	
Test of Everyday Cognitive Ability*		X		X		X	
Grip Strength*		X		X		X	
Grooved Pegboard*		X		X		X	
Positive and Negative Affect Scale (PANAS)*		X	X	X	X	X	
Visual analog scale for		X	X	X	X	X	

fatigue (pre- and post-session)							
Visual analog scale for pain (pre-, early-, mid- and post-session)		X	X	X	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		X		
Daily assessment of sleep			X		X		
Patient and Caregiver Questionnaires*						X	
Participant Evaluation of Study Procedures*			X	X	X	X	
Count of successful tDCS sessions (confirmation code by session days)			X	X	X	X	
Optional measures that may be excluded based on study personnel judgement are indicated by an asterisk.							

e)***Analytic Plan:***

Specific Aim 1 is to determine feasibility; to be measured by the number of participants successfully completed using the proposed protocol for training and monitored administration. As would be expected, there is a high rate of compliance for in-clinic tDCS administration and therefore remotely-supervised administration should be designed to be similarly compliant. Study success will be defined by 80% participants having completed 80% sessions, shown to be the target compliance for previous tDCS studies[107] . We will also determine the effectiveness of our sham procedures to ensure blinding, as tested by comparing those who accurately identified the sham condition. We will assess whether the frequency or type of side effects differ between the active and control conditions and whether they occur at the same rate as reported from studies of in-clinic administration. *Secondary outcomes* will be tolerability, participant-reported adverse events, and comparisons of active and control conditions on these measures.

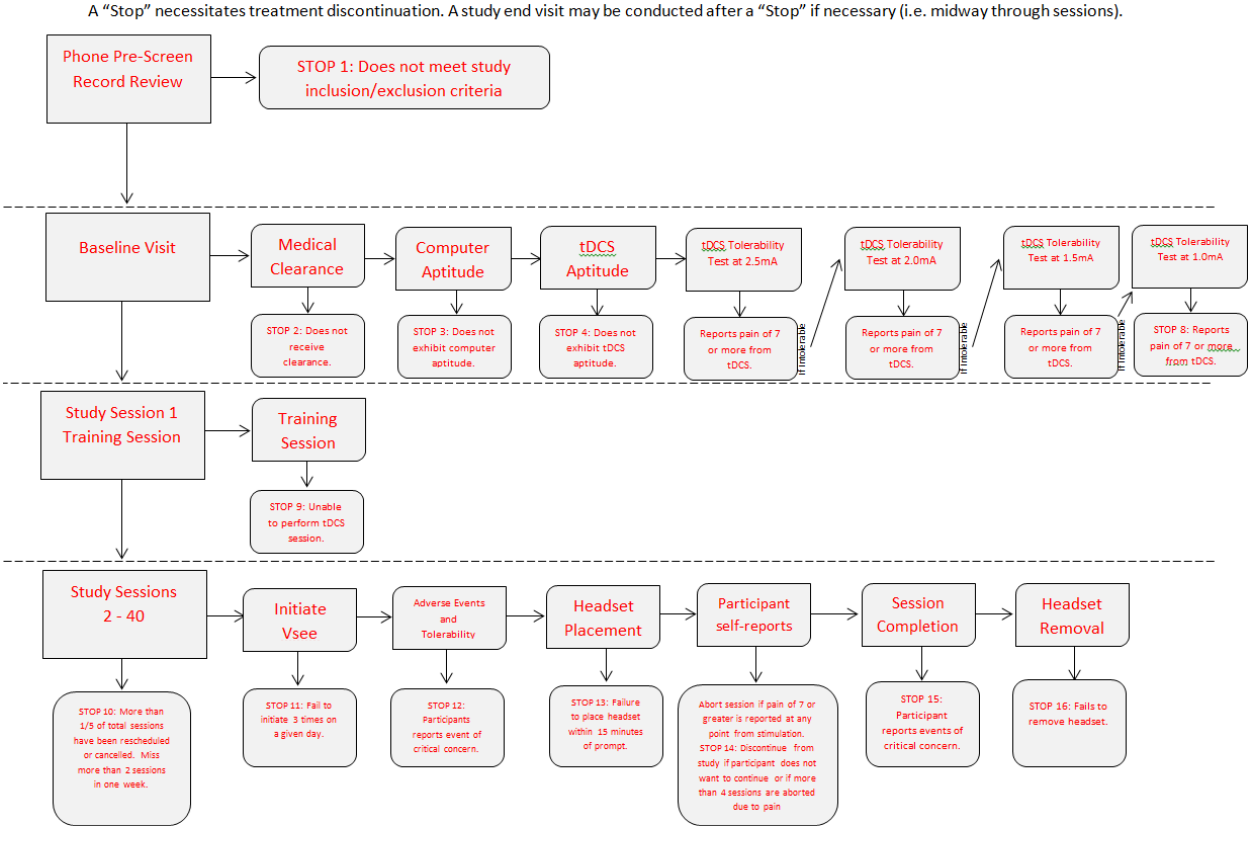
Specific Aim 2 will be to determine preliminary signals for efficacy, and to have pilot findings to determine necessary sample sizes for an adequately-powered clinical trial. For each participant, change scores will be calculated between baseline and study end scores on measures of fatigue and cognitive functioning. These difference scores will then be described and compared between groups (t-tests and ANOVA related analyses) to determine signals of efficacy for active tDCS paired with cognitive remediation vs. active tDCS paired with non-adaptive puzzle and board games vs. sham tDCS paired with cognitive remediation.

VI. METHODS AND PROCEDURES

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). Following state of the art in tDCS research, devices will be programmed in advance by the PI to provide either active or sham sessions following current standards for blinding[33, 108]. During a sham session, the device is programmed to ramp up to the desired intensity (target 2.5 mA) and ramp down for the initial 60 seconds, with no current delivery during the following 18 minutes of the session, and then current is ramped up and down for 60 seconds at the end of the session. These brief periods of stimulation serve to mimic the effects of a true stimulation session. Both participants and study coordinator (who administers study outcome measures) will be blinded, and will be asked to guess the assigned condition at study end.

The PI will not be blinded to study condition. The PI or an un-blinded study technician will preprogram devices according to randomization and then provide to the study coordinator for each participant. That is, the study coordinator and participant will be blinded to which condition programmed to the assigned device. All procedures will be the same for all three conditions. Adverse events will be addressed in either condition, and the study PI will always know the assigned condition for each participant.

Figure 2. Study stop criteria



Screening:

Participants for all groups will be recruited from the NYU Langone Medical Center Multiple Comprehensive Care Center. Once a potential participant is identified, a screening phone call will take place to determine general eligibility (See section IX. Consent Process). Once a participant is deemed generally eligible, the individual will be scheduled for a visit at NYU to review and sign consent and complete screening procedures, including a medical clearance. For those interested in study participation, once eligibility is confirmed by a NYU MS Center clinician, their baseline appointment will be scheduled.

Baseline Visit:

***Note clinician assessment for medical clearance may occur either before or at the baseline visit**

All women who are of child-bearing age will complete a pregnancy test (human chorionic gonadotrophin urine assay) to assure they are eligible for all study procedures. Women who receive a result denoting heightened hCG levels will be considered study screen failures.

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, they 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, followed by a 30-second ramp down. The tolerability test will first take place using 2.5 mA stimulation. If the participant tolerates and agrees, 2.5 mA will be used for all following stimulation sessions. Alternatively, if the participant cannot tolerate 2.5 mA, stimulation will be based on highest amplitude tolerated, following 0.5 mA decrements (2.0, 1.5., and 1.0 mA.) till finally a base 1.0 mA stimulation is offered. Once the tolerable dose is established, it will remain constant throughout the study. If the participant cannot tolerate any of the offered stimulation levels, they are excluded from the study.

Remotely Monitored Study Sessions 2 to 40:

These sessions will be completed from home with remote monitoring by the study technician. For participants in the sham condition who elect 10 additional sessions of the open-label, active tDCS, these same procedures will be repeated.

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 a secure internet-based video program.

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.

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.

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.

Online/Telephone Survey:

One month following the study end visit, participants will receive an online survey to complete through REDcap. This survey will consist of a text box to enter delayed recall words from the RAVLT task completed at follow-up, as well as the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ), PROMIS Measure of Fatigue, Mood and Health-Related Quality of Life, Neuro-Quality of Life measures, the Fatigue Impact Scale, the Fatigue Severity Scale, and the Positive and Negative Affect Scale (PANAS). In addition to these 7 measures, participants will be asked to assess their experience with the study:

> "Overall, did you feel a benefit from participating in this trial? If so, how? If so, has the benefit lasted?"

All data will be entered into REDcap, either directly by participants if they select to complete the measures online, or by research assistants if the participants select to complete the measures in an interview format via phone.

Open label tDCS Sessions:

Following the study end visit, individuals in the sham condition will be offered 10 open-label active tDCS sessions.

VII. SUBJECT SELECTION

Characteristics of the Research Population

We will enroll a total of n=85 adults (ages 18 and over) with confirmed MS. Participation will be open to those with all subtypes and levels of disability who meet the eligibility criteria as below.

Eligibility Criteria

Enrolled participants must have a diagnosis of MS (any subtype) with stable disease status and expanded disability status scale (EDSS) [89] scores of less than 6.5 or above with proxy. Individuals with a Symbol Digit Modalities Test or SDMT [105] score ≥3.0 SD below published norms will be excluded as will those with any health condition contraindicated with the use of a tDCS device (including history of seizures, abnormal EKG, skin disorders, head trauma or medical device in the head or neck). Baseline screening evaluation will include a neurological exam and medical clearance by the study physician and brief screening evaluations for ability to operate the study equipment.

Inclusion Criteria	Exclusion Criteria

• Ages 18-79 • Definite MS diagnosis, all subtypes [95] • MS-related changes in cognitive functioning* • A score of 6.5 or lesson the Expanded Disability Status Scale (EDSS) OR more than 6.5 with proxy • Has stable and continuous access to internet service at home compatible with the study laptop (Wi-Fi or ethernet cable) • Adequate internet capacity for remote monitoring, as tested by http://www.speedtest.net/) • Adequate home facilities (enough space, access to quiet and distraction free area)	• 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 neurologist or study staff • Relapse or steroid use in previous month • History of mental retardation, pervasive developmental disorder or other neurological condition associated with cognitive impairment • Primary psychiatric disorder that would influence ability to participate • History of seizures or seizure disorder

• Able to commit to the two-week period of training sessions with baseline and follow-up visits. • Able to understand the informed consent process and provide consent to participate in the study	• History of head trauma (e.g., head injury, brain surgery) in the past year or 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 • History of uncontrolled or labile hypertension. • Other serious uncontrolled medical condition (e.g., cancer or acute myocardial infarction) • History of clinically significant abnormalities on electrocardiogram (EKG) • Alcohol or other substance use disorder • Learned English language after 12 years of age • Pregnant or breastfeeding • Symbol Digit Modalities Test ≥3.0 SD below published norms

Gender and Minority Inclusion of Subjects

Gender and minority inclusion for this project will be promoted in several ways. Enrollment will primarily be through the NYU MS Comprehensive Care Center, with a diverse patient The Health Initiative for Underserved Communities and members of its Community Health Advisory Board will be informed of the project and asked to make their members aware of eligibility.

Vulnerable Subjects

Participants with MS may be considered as vulnerable subjects due to cognitive impairment; 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 care provided at 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 to their decision not to participate.

VIII. STUDY LOCATION

Participants screening, baseline and study end visits will be completed at the NYU MS 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, 180 E Pulaski Rd, Huntington Station, NY 11746. For participants with limited mobility, visits can be completed from the participant's home.

IX. 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.

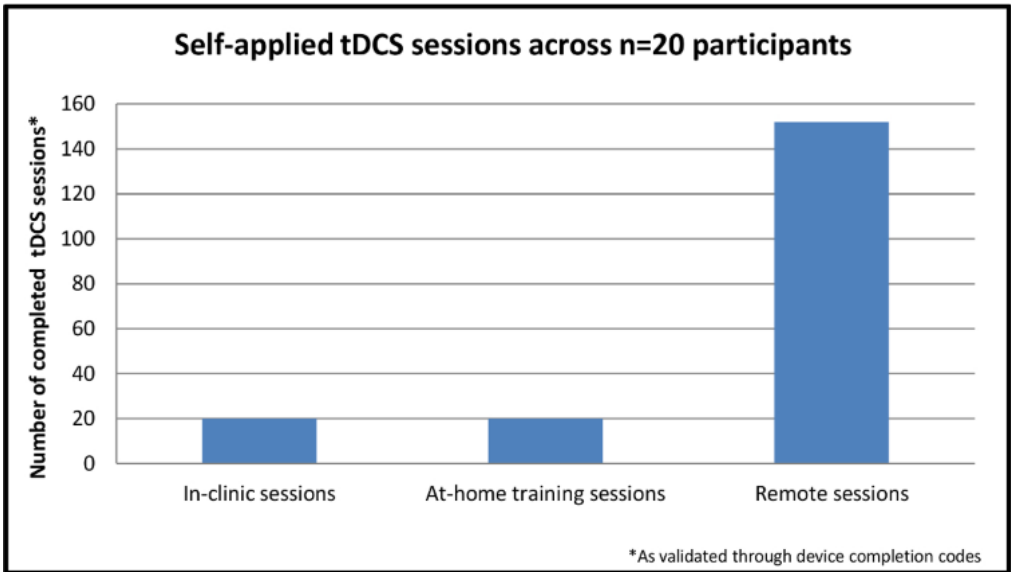
Monitoring

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. Co-investigators, and study coordinator. 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 10 subjects the compliance is significantly less in one or more arm of the study relative to our previously observed compliance rates, 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. Therefore, this discrepancy in compliance is not expected. We would define discrepancy in compliance as >50% difference in mean number of visits completed and/or 50% difference in number of "completers" in each condition (defined by completing at least 50% of n=5/10 sessions) [109]. If there is significantly poor compliance in the active session, 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.

An adverse event is defined as any rating (at any time) of pain of greater than "moderate" or side effects or sensations that arise preceding, during, or following stimulation. Pain and tolerability are measured before, during and after each session. As noted, there is an extensive body of literature demonstrating the safety and tolerability of tDCS both in MS and in a range of clinical disorders. Our lab at Stony Brook Medicine administered >200 active tDCS sessions to MS participants with no pain ratings of severe or greater and no discontinued session (for any reason, safety or tolerability)[109]. Figure 3 below demonstrates these results.

Figure 3. Self-applied tDCS sessions across n=20 participants[109]



We will submit study data safety monitoring reports to the IRB after 10 participants are enrolled in the active condition, 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.

Specific Aim 1 will be tested by comparing the number of participants in each condition meeting the study definition of compliance (having completed 80% sessions). We will also determine the effectiveness of our sham procedures to ensure blinding, as tested by comparing those who accurately identified the sham condition. We will assess whether the frequency or type of side effects differ between the three conditions and whether they occur at the same rate as reported from studies of in-clinic administration.

Specific Aim 2 will be to determine preliminary signals for efficacy, and to have pilot findings to determine necessary sample sizes for an adequately-powered clinical trial. For each participant, change scores will be calculated between baseline and study end scores on measures of fatigue and cognitive functioning. These difference scores will then be described and compared between groups (t-tests and ANOVA related analyses) to determine signals of efficacy.

Cognitive performance will be evaluated for those who completed at least 18 sessions. We conservatively plan for comparison of 15 participants in each group, allowing for up to 33% dropout. While both cognitive remediation groups are expected to improve with cognitive training, we hypothesize that the active tDCS condition will gain one standard deviation (of the published normative mean) or more in score than the sham condition and that the group with active tDCS paired with non-adaptive puzzle and board games will neither improve nor decline.

Secondary outcomes will be used to compare the groups in change in performance on the additional measures listed in Table 2. These are the most commonly-used outcome measures in MS trials[52, 106, 112, 113]. While important to include, they will not be the primary outcome due to strong susceptibility of improvement with practice effects over repeated administrations in MS samples[52, 113-116]. 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, parameters shown to improve with tDCS[44]. Similar analysis as what have been planned for the primary outcome will be performed for comparing the change in these secondary outcomes between two groups.

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

X. SUBJECT RECRUITMENT AND CONSENT/ASSENT

Subject Identification, Recruitment and Consent/Assent

Method of Subject Identification and Recruitment

The MS Comprehensive Care Center of NYU Langone Medical Center has an extensive recruitment base. Patients will be recruited to participate in studies from all over New York and the other continental United States. 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 and sub-investigators. All physicians and medical staff at the MS Care Center will be presented with the study description. A patient who is seeing one of these medical staff members as their treating physician will be introduced to the study by that medical staff member. 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 MS related websites.

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. This phone screen is minimal risk to the participant and collected information will be maintained in secured, locked files. De-identified information (assigned a study screening code) will be entered into a secure, NYU approved online screening database. 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.

Dr. Lauren Krupp 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. Dr. Krupp and team at the MS Center are MS specialists with extensive experience in the assessment of patients with MS, including cognitive capacity, and 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.

Dr. Krupp is an internationally renowned expert of cognition in MS. She has the expertise in MS and cognitive related symptoms of MS to specifically be capable of determining cognitive capacity of potential participants. She is a professor of neurology and the director of the NYU MS Center. She has over 30 years of experience with direct clinical care of MS patients, and is an internationally-recognized expert in the area of MS symptomatic management. She has served as PI for numerous investigator-initiated federally-funded clinical trials in MS as well as industry-sponsored treatment trials. She has authored over 150 articles on topics directly related to the current project. Dr. Krupp also served in the same medical monitoring role for the pilot study at Stony Brook Medicine, where n=23 patients have successfully completed our study protocol that has included over 200 active tDCS sessions.

Participants will be informed of the assessment and consequences of the assessment – those who refuse the capacity assessment will not be enrolled. The assessment involves a MS Neurological Examination including EDSS, Physical Examination summary to address General, HEENT, Lungs, COR, Abdomen, Extremities, and Skin. Additionally, Dr. Krupp will base capacity to consent on the participants understanding of the following 4 items a) that the activity described in this consent document constitutes research, not standard treatment, b) the risks and benefits of this study c) the alternatives that are available if s/he chooses not to participate, and d) that the decision to not participate will be accepted without penalty, i.e., without jeopardizing his/her clinical care.

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 co-investigators 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 Dr. Lauren Krupp 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
There will be no cost to the participants.

Risk to Participants
As described above, tDCS poses low risks to participants and our protocol is well-tolerated. 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 IDE. Because of its prior designation of tDCS devices as 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-signficant-risk by IRB review which provide its 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 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 IDE for current ongoing studies at this institution.

The safety of this technique has been addressed and tested by multiple researchers (e.g., Hummel, et al.[117]; Fregni, et. al.[19, 118]; Nitsche, et al. [13, 24, 119]; Priori, et al.[120]) 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.[19] 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[121]. 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[122] 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 cognitive training sessions (brain training games) may enhance cognitive functioning for all groups. Additionally, participants in the active tDCS condition, as well as those in the sham condition who elect for 10 open label sessions at study end, may have an increase in cognitive functioning through the use of the tDCS device. We hope the knowledge gained from this study will help others with MS in the future.

Payment for Participation

Participant will receive up to $100 in total compensation. They will be compensated $50 for the initial screening and baseline visit, and $50 for the follow-up visit. Attempted completion of a study session will be defined by signing in to the secure internet-based video for contact with study technician within 15 minutes of scheduled time for all days of remote contact. If the participant is unable to establish video contact with the study technician due to technical difficulties, they must contact the study technician by phone by the scheduled time to receive credit for effort.

XI. EXPLORATORY AIM: FEASIBILITY IN PARKINSON'S DISEASE

Purpose

We have established the feasibility and safety of the current protocol in MS and now plan to extend its use to other neurological disorders. The purpose of this additional aim is to test the feasibility of the

established remotely supervised in-home self-administered tDCS combined with computerized cognitive activities in Parkinson's disease (PD) patients.

Background

Parkinson's disease is the second leading neurodegenerative disease and affects near 5.1 million Americans. Clinical trials in PD have relatively low rates of success. Investigators face major challenges, mostly in recruitment and retention of participants, largely due to the difficulty maintaining compliance from a patient suffering from PD. Common symptoms in PD that potentially interfere with compliance include poor mobility, impaired equilibrium, fatigue, mood disorder, lack of motivation (apathy) and fear of the potential adverse consequences/side effects of taking part in clinical trials.

The safety profile, tolerability, and ease of applicability of conventional tDCS are very well established and are promising technical strengths that could lead to a complementary therapy in PD. Conventional tDCS therapy in PD has yielded promising results improving executive function[22], gait [123-125], motor impairment[126-128], and cognitive impairment[129, 130]

However, similar to protocols with MS, sample sizes are limited, as are the number of tDCS sessions due to the requirement to make repeated visits to clinic, with some studies including just eight participants [124] and the largest including just 25 participants[128]. Adequately powered, sham-controlled clinical trials are needed to ascertain real therapeutic applications and we hope to establish a remotely-supervised protocol to guide future studies using tDCS in PD

For this Exploratory Aim, remote tDCS feasibility in Parkinson's disease, the protocol will be open label and mirrored for the active tDCS condition. We initially plan enrolling 30 participants with PD

Exploratory Aim

<u>Exploratory Aim</u>: We will test the feasibility of remotely-supervised in-home self-administered tDCS combined with computerized cognitive activities in Parkinson's Disease (PD). Participants (n=30) will be trained to administer active tDCS and complete a cognitive training activity in their home under remote supervision by study staff.
<u>Hypothesis 1</u>: Remotely-supervised in-home delivery of the tDCS combined with computerized cognitive activity is a safe and feasible treatment for impairment in Parkinson's disease. Primary outcome will be number of days of successful tDCS delivery. Secondary outcomes will be tolerability and participant-reported adverse events, fatigue and mood.

Description of the protocol

Will mirror the exact protocol detailed in section **V**, however this study will be an open label feasibility study, with all participants receiving active, open-label tDCS. There will be no sham condition for the PD aim.

Methods and Procedures

Will mirror the exact methods detailed in section **VI**, with the exception that this study will be an open label feasibility study, with all participants receiving active, open-label tDCS. The exploratory aim to test the methods in a PD population will also run for a shorter duration. The treatment will occur over the course of 10 days rather than 40 to test initial feasibility of the methods in PD. Participants will attend the initial baseline visit in clinic, with the remaining 9 sessions occurring from home with remote supervision.

PD Specific Outcome Measures: Before and after each session, participants will complete brief measures to monitor for any stimulation-related events as well as mood and fatigue. In addition, a pain scale will be administered during the session. Participants will also complete baseline and study-end inventories of mood and fatigue and complete a brief battery of cognitive tests, to help guide power estimates for the future trials. A summary of outcome measures can be found in Table 3.

Table 3

Test	Screening	Baseline	Daily Study Sessions (2-10)	End of Study Session	Online/ Telephone Survey (Study end date + 1 month)
Medical Clearance	X				
Expanded Disability Status Scale	X			X	
Wide Range Achievement Test (WRAT-4)	X	X			
Symbol Digit Modalities Test (SDMT)	X	X		X	
Beck Depression Inventory-Fast Screen		X		X	
tDCS Aptitude Test		X			
tDCS Tolerance Test (2.0 mA, will possibility to repeat at 1.5 mA)		X			
Multiple Sclerosis Neuropsychological Questionnaire (MSNQ)		X		X	X
PROMIS Measure of Fatigue, Mood and Health-Related Quality of Life		X		X	X
Neuro-Quality of Life		X		X	X
Fatigue Impact Scale		X		X	X
Fatigue Severity Scale		X		X	X
Pittsburgh Fatigability Scale		X		X	

Attention Network Test-Interaction		X		X	
Cogstate Brief Battery		X		X	
ERTSLab Processing Battery		X	X	X	
Controlled Oral Word Association		X		X	
Rey Auditory Verbal Learning Test		X		X	X (delayed recall only)
Brief Visuospatial Memory Test- Revised		X		X	
King Devick Test		X		X	
Test of Everyday Cognitive Ability		X		X	
Grip Strength		X		X	
Grooved Pegboard		X		X	
Positive and Negative Affect Scale (PANAS)		X	X	X	
Visual analog scale for fatigue (pre- and post-session)		X	X	X	
Visual analog scale for pain (pre-, early-, mid- and post-session)		X	X	X	
Tolerability questionnaire - administered by study staff (pre- and post-session)			X		
Safety and tolerability questionnaire –self-report (pre- and post-session)			X		
Score for Computerized cognitive games (daily)			X		
UPDRS		X		X	X*
CG S/I		X		X	X
PDQ-39		X		X	X
Parkinson's Fatigue Scale (PFS-16)		X		X	
Daily assessment of sleep			X		

Patient and Caregiver Questionnaires			X		
Participant Evaluation of Study Procedures			X	X	
Count of successful tDCS sessions (confirmation code by session days)			X	X	

* Only UPDRS Part 2: Self-assessment of activities of daily living.

Subject Selection

Characteristics of the Research Population

We will enroll a total of n=30 adults (30-89) with confirmed Parkinson's disease. Participation will be open to those with all levels of disability who meet the eligibility criteria as below.

Eligibility Criteria

Enrolled participants must have a diagnosis of Parkinson's disease confirmed by a neurologist with expertise in Movement Disorders.

Patients with a Symbol Digit Modalities Test or SDMT[105] score ≥3.0 SD below published norms will be excluded as will those with any health condition contraindicated with the use of a tDCS device (including history of seizures, abnormal EKG, skin disorders, head trauma or medical device in the head or neck). Baseline screening evaluation will include a neurological exam and medical clearance by the study physician and brief screening evaluations for ability to operate the study equipment.

Parkinson's Inclusion Exclusion table here:

Inclusion	**Exclusion**

● Ages 30-89 ● PD diagnosis confirmed by Movement Disorder specialist ● Has stable and continuous access to internet service at home compatible with the study laptop (Wi-Fi or ethernet cable) ● Adequate internet capacity for remote monitoring, as tested by http://www.speedtest.net/) ● Adequate home facilities (enough space, access to quiet and distraction free area) ● Able to commit to the two-week period of training sessions with baseline and follow-up visits. ● Able to understand the informed consent process and provide consent to	● 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 neurologist or study staff ● History of seizures or seizure disorder ● Current uncontrolled chronic headaches or migraines. In addition, if a subject has had a change in the rate or severity of head pressure, headache, or migraine in the past two weeks, they are excluded. ● History of head trauma (e.g., head injury, brain surgery) in the past year or 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

participate in the study	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 ● History of uncontrolled or labile hypertension. ● Other serious uncontrolled medical condition (e.g., cancer or acute myocardial infarction) ● History of clinically significant abnormalities on electrocardiogram (EKG) ● Alcohol or other substance use disorder ● Learned English language after 12 years of age ● Pregnant or breastfeeding ● Symbol Digit Modalities Test ≥3.0 SD below published norms

Study Location

Participants screening, baseline and study end visits will be completed at the Fresco Institute for Parkinson's Disease and Movement Disorders at NYU Langone Medical Center, 240 East 38th Street, 20th Floor, NY, NY 10016; or alternatively at the 18th floor, the NYU Langone MS Comprehensive Care Center (240 East 38th Street, 18th Floor, NY NY 10016). For participants with limited mobility, visits can be completed from the participant's home.

Data Analyses and Data Monitoring

These items will mirror exactly the procedures detailed in section IX, with the exception of the Statistical Analyses (detailed below)

Statistical Analyses

Data analyses will be descriptive to inform protocol development for a larger controlled clinical trial. To determine feasibility of number of days of successful administration will be calculated. Any participants who fail either an aptitude or tolerability test at baseline will be characterized with clinical and cognitive factors.

Subject Identification, Recruitment and Consent/Assent

Method of Subject Identification and Recruitment

The Fresco Institute for Parkinson's Disease and Movement Disorders of NYU Langone Medical Center has an extensive recruitment base. Patients will be recruited to participate in studies from

all over New York and the other continental United States. 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 and sub-investigators. All physicians and medical staff at Fresco Institute will be presented with the study description. A patient who is seeing one of these medical staff members as their treating physician will be introduced to the study by that medical staff member. 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 and medically cleared.

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 Fresco Institute related websites.

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. This phone screen is minimal risk to the participant and collected information will be maintained in secured, locked files. De-identified information (assigned a study screening code) will be entered into a secure, NYU approved online screening database. 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.

Dr. Agarwal 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 and other neurological diseases, including the work in our lab at Stony Brook Medicine, show tDCS to be a tolerable and safe treatment approach. Dr. DiRocco and team at the Fresco Institute for Parkinson's and Movement Disorders in the Department of Neurology at NYU are movement disorder specialists with extensive experience in the assessment of patients with Parkinson's disease, including cognitive capacity, and 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. Additionally, Drs. Biagioni and Shashank will base capacity to consent on the participants understanding of the following 4 items a) that the activity described in this consent document constitutes research, not standard treatment, b) the risks and benefits of

this study c) the alternatives that are available if s/he chooses not to participate, and d) that the decision to not participate will be accepted without penalty, i.e., without jeopardizing his/her clinical care.

Process to Document Consent in Writing, Subject Capacity, Debriefing Procedures, Consent Forms, Documentation of Consent, Costs to the Subject, Risk to Participants, Benefits to Participants, and Payment for Participation

These items will mirror exactly the procedures detailed in section X.

1. Kasschau.M. CL, Sherman K., Haider L., Frontario A., Krupp L., Datta A., Bikson M,. A Protocol for the Use of Remotely-Supervised Transcranial Direct Current Stimulation in Clinical Trials in Multiple Sclerosis (MS). Journal of Visualized Experiments 2015 (In Press).
2. Frohman EM, Racke MK, Raine CS. Multiple sclerosis--the plaque and its pathogenesis. The New England journal of medicine 2006;354:942-955.
3. Siffrin V, Vogt J, Radbruch H, Nitsch R, Zipp F. Multiple sclerosis - candidate mechanisms underlying CNS atrophy. Trends in neurosciences 2010;33:202-210.
4. Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. Brain : a journal of neurology 2006;129:606-616.
5. Poser CM, Brinar VV. The accuracy of prevalence rates of multiple sclerosis: a critical review. Neuroepidemiology 2007;29:150-155.
6. Adelman G, Rane SG, Villa KF. The cost burden of multiple sclerosis in the United States: a systematic review of the literature. Journal of medical economics 2013;16:639-647.
7. Fregni F, Nitsche MA, Loo CK, et al. Regulatory Considerations for the Clinical and Research Use of Transcranial Direct Current Stimulation (tDCS): review and recommendations from an expert panel. Clinical research and regulatory affairs 2015;32:22-35.
8. Brunoni AR, Nitsche MA, Bolognini N, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain stimulation 2012;5:175-195.
9. Bikson M, Inoue M, Akiyama H, et al. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. The Journal of physiology 2004;557:175-190.
10. Datta A, Zhou X, Su Y, Parra LC, Bikson M. Validation of finite element model of transcranial electrical stimulation using scalp potentials: implications for clinical dose. Journal of neural engineering 2013;10:036018.
11. Bikson M, Datta A. Guidelines for precise and accurate computational models of tDCS. Brain stimulation 2012;5:430-431.
12. Hunter MA, Coffman BA, Gasparovic C, Calhoun VD, Trumbo MC, Clark VP. Baseline effects of transcranial direct current stimulation on glutamatergic neurotransmission and large-scale network connectivity. Brain research 2015;1594:92-107.
13. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 2001;57:1899-1901.
14. Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum 2011;14:1133-1145.
15. Vanneste S, Plazier M, Ost J, van der Loo E, Van de Heyning P, De Ridder D. Bilateral dorsolateral prefrontal cortex modulation for tinnitus by transcranial direct current stimulation: a preliminary clinical study. Experimental brain research 2010;202:779-785.
16. Priori A, Hallett M, Rothwell JC. Repetitive transcranial magnetic stimulation or transcranial direct current stimulation? Brain stimulation 2009;2:241-245.
17. Nitsche MA, Boggio PS, Fregni F, Pascual-Leone A. Treatment of depression with transcranial direct current stimulation (tDCS): a review. Experimental neurology 2009;219:14-19.
18. Vigod S, Dennis CL, Daskalakis Z, et al. Transcranial direct current stimulation (tDCS) for treatment of major depression during pregnancy: study protocol for a pilot randomized controlled trial. Trials 2014;15:366.
19. Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology 2005;64:872-875.

20. Demirtas-Tatlidede A, Vahabzadeh-Hagh AM, Pascual-Leone A. Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders? Neuropharmacology 2013;64:566-578.
21. Borckardt JJ, Bikson M, Frohman H, et al. A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. The journal of pain : official journal of the American Pain Society 2012;13:112-120.
22. Doruk D, Gray Z, Bravo GL, Pascual-Leone A, Fregni F. Effects of tDCS on executive function in Parkinson's disease. Neuroscience letters 2014;582:27-31.
23. Bikson M, Name A, Rahman A. Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms. Frontiers in human neuroscience 2013;7:688.
24. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. The Journal of physiology 2000;527 Pt 3:633-639.
25. Monte-Silva K, Kuo MF, Hessenthaler S, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain stimulation 2013;6:424-432.
26. Scheldrup M, Greenwood PM, McKendrick R, et al. Transcranial direct current stimulation facilitates cognitive multi-task performance differentially depending on anode location and subtask. Frontiers in human neuroscience 2014;8:665.
27. McIntire LK, McKinley RA, Goodyear C, Nelson J. A comparison of the effects of transcranial direct current stimulation and caffeine on vigilance and cognitive performance during extended wakefulness. Brain stimulation 2014;7:499-507.
28. Nelson JT, McKinley RA, Golob EJ, Warm JS, Parasuraman R. Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). NeuroImage 2014;85 Pt 3:909-917.
29. Elmasry J, Loo C, Martin D. A systematic review of transcranial electrical stimulation combined with cognitive training. Restorative neurology and neuroscience 2015.
30. Brunoni AR, Vanderhasselt MA. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain and cognition 2014;86:1-9.
31. Meesen RL, Thijs H, Leenus DJ, Cuypers K. A single session of 1 mA anodal tDCS-supported motor training does not improve motor performance in patients with multiple sclerosis. Restorative neurology and neuroscience 2014;32:293-300.
32. Shiozawa P, Fregni F, Bensenor IM, et al. Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum 2014;17:1443-1452.
33. Loo CK, Alonzo A, Martin D, Mitchell PB, Galvez V, Sachdev P. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. The British journal of psychiatry : the journal of mental science 2012;200:52-59.
34. Martin DM, Liu R, Alonzo A, et al. Can transcranial direct current stimulation enhance outcomes from cognitive training? A randomized controlled trial in healthy participants. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum 2013;16:1927-1936.
35. Tecchio F, Cancelli A, Cottone C, et al. Multiple sclerosis fatigue relief by bilateral somatosensory cortex neuromodulation. Journal of neurology 2014;261:1552-1558.
36. Mori F, Ljoka C, Magni E, et al. Transcranial magnetic stimulation primes the effects of exercise therapy in multiple sclerosis. Journal of neurology 2011;258:1281-1287.
37. Saiote C, Goldschmidt T, Timaus C, et al. Impact of transcranial direct current stimulation on fatigue in multiple sclerosis. Restorative neurology and neuroscience 2014;32:423-436.
38. Ferrucci R, Vergari M, Cogiamanian F, et al. Transcranial direct current stimulation (tDCS) for fatigue in multiple sclerosis. NeuroRehabilitation 2014;34:121-127.
39. Mori F, Codeca C, Kusayanagi H, et al. Effects of anodal transcranial direct current stimulation on chronic neuropathic pain in patients with multiple sclerosis. The journal of pain : official journal of the American Pain Society 2010;11:436-442.
40. Mori F, Nicoletti CG, Kusayanagi H, et al. Transcranial direct current stimulation ameliorates tactile sensory deficit in multiple sclerosis. Brain stimulation 2013;6:654-659.
41. Charvet L, Shaw M, Haider L, Melville P, Krupp L. Remotely-delivered cognitive remediation in multiple sclerosis (MS): protocol and results from a pilot study. Multiple Sclerosis Journal – Experimental, Translational and Clinical 2015;1.

42. Charvet LE KM, Bikson M, Datta A, Knotkova H, Stevens MC, Alonzo A, Loo C, Krull K, Haider L. . Remotely-Supervised Transcranial Direct Current Stimulation (tDCS). . NYC Neuromodulation Conference; 2015; New York, NY.
43. Palm U, Ayache SS, Padberg F, Lefaucheur JP. Non-invasive Brain Stimulation Therapy in Multiple Sclerosis: A Review of tDCS, rTMS and ECT Results. Brain stimulation 2014;7:849-854.
44. Mattioli F, Bellomi F, Stampatori C, Capra R, Miniussi C. Neuroenhancement through cognitive training and anodal tDCS in multiple sclerosis. Multiple sclerosis 2015.
45. Bobholz JA, Rao SM. Cognitive dysfunction in multiple sclerosis: a review of recent developments. Current opinion in neurology 2003;16:283-288.
46. Jonsson A, Andresen J, Storr L, Tscherning T, Soelberg Sorensen P, Ravnborg M. Cognitive impairment in newly diagnosed multiple sclerosis patients: a 4-year follow-up study. Journal of the neurological sciences 2006;245:77-85.
47. Smerbeck AM, Parrish J, Serafin D, et al. Visual-cognitive processing deficits in pediatric multiple sclerosis. Multiple sclerosis 2011;17:449-456.
48. Figved N, Myhr KM, Larsen JP, Aarsland D. Caregiver burden in multiple sclerosis: the impact of neuropsychiatric symptoms. Journal of neurology, neurosurgery, and psychiatry 2007;78:1097-1102.
49. Strober LB, Christodoulou C, Benedict RH, et al. Unemployment in multiple sclerosis: the contribution of personality and disease. Multiple sclerosis 2012;18:647-653.
50. Achiron A, Chapman J, Magalashvili D, et al. Modeling of cognitive impairment by disease duration in multiple sclerosis: a cross-sectional study. PloS one 2013;8:e71058.
51. Hankomaki E, Multanen J, Kinnunen E, Hamalainen P. The progress of cognitive decline in newly diagnosed MS patients. Acta neurologica Scandinavica 2014;129:184-191.
52. Glanz BI, Healy BC, Hviid LE, Chitnis T, Weiner HL. Cognitive deterioration in patients with early multiple sclerosis: a 5-year study. Journal of neurology, neurosurgery, and psychiatry 2012;83:38-43.
53. Rocca MA AM, De Stefano N, Enzinger C, Geurts JJ, Penner, IK, Rovira A, Sumowski JF, Valasina P, Filippi M. Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. The Lancet Neurology 2015;Published online 2.5.15.
54. Amato MP, Langdon D, Montalban X, et al. Treatment of cognitive impairment in multiple sclerosis: position paper. Journal of neurology 2013;260:1452-1468.
55. Lyros E, Messinis L, Papageorgiou SG, Papathanasopoulos P. Cognitive dysfunction in multiple sclerosis: the effect of pharmacological interventions. International review of psychiatry 2010;22:35-42.
56. Kappos L, Freedman MS, Polman CH, et al. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. Lancet 2007;370:389-397.
57. Kappos L, Freedman MS, Polman CH, et al. Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. The Lancet Neurology 2009;8:987-997.
58. Derfuss T, Kappos L. Evaluating the potential benefit of interferon treatment in multiple sclerosis. Jama 2012;308:290-291.
59. Fischer JS, Priore RL, Jacobs LD, et al. Neuropsychological effects of interferon beta-1a in relapsing multiple sclerosis. Multiple Sclerosis Collaborative Research Group. Annals of neurology 2000;48:885-892.
60. Krupp LB, Christodoulou C, Melville P, Scherl WF, MacAllister WS, Elkins LE. Donepezil improved memory in multiple sclerosis in a randomized clinical trial. Neurology 2004;63:1579-1585.
61. Christodoulou C, Melville P, Scherl WF, Macallister WS, Elkins LE, Krupp LB. Effects of donepezil on memory and cognition in multiple sclerosis. Journal of the neurological sciences 2006;245:127-136.
62. Krupp LB, Christodoulou C, Melville P, et al. Multicenter randomized clinical trial of donepezil for memory impairment in multiple sclerosis. Neurology 2011;76:1500-1507.
63. Morrow SA, Kaushik T, Zarevics P, et al. The effects of L-amphetamine sulfate on cognition in MS patients: results of a randomized controlled trial. Journal of neurology 2009;256:1095-1102.
64. Benedict RH, Munschauer F, Zarevics P, et al. Effects of l-amphetamine sulfate on cognitive function in multiple sclerosis patients. Journal of neurology 2008;255:848-852.
65. Heal DJ, Smith SL, Gosden J, Nutt DJ. Amphetamine, past and present--a pharmacological and clinical perspective. Journal of psychopharmacology 2013;27:479-496.
66. Stuifbergen AK, Becker H, Perez F, Morison J, Kullberg V, Todd A. A randomized controlled trial of a cognitive rehabilitation intervention for persons with multiple sclerosis. Clinical rehabilitation 2012;26:882-893.

67. O'Brien AR, Chiaravalloti N, Goverover Y, Deluca J. Evidenced-based cognitive rehabilitation for persons with multiple sclerosis: a review of the literature. Archives of physical medicine and rehabilitation 2008;89:761-769.
68. Chiaravalloti ND, Moore NB, Nikelshpur OM, DeLuca J. An RCT to treat learning impairment in multiple sclerosis: The MEMREHAB trial. Neurology 2013;81:2066-2072.
69. Rosti-Otajarvi EM, Hamalainen PI. Neuropsychological rehabilitation for multiple sclerosis. The Cochrane database of systematic reviews 2011:CD009131.
70. Lampit A, Hallock H, Valenzuela M. Computerized cognitive training in cognitively healthy older adults: a systematic review and meta-analysis of effect modifiers. PLoS medicine 2014;11:e1001756.
71. Nahum M, Lee H, Merzenich MM. Principles of neuroplasticity-based rehabilitation. Progress in brain research 2013;207:141-171.
72. Mishra J, de Villers-Sidani E, Merzenich M, Gazzaley A. Adaptive training diminishes distractibility in aging across species. Neuron 2014;84:1091-1103.
73. Merzenich MM, Van Vleet TM, Nahum M. Brain plasticity-based therapeutics. Frontiers in human neuroscience 2014;8:385.
74. Vinogradov S, Fisher M, de Villers-Sidani E. Cognitive training for impaired neural systems in neuropsychiatric illness. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 2012;37:43-76.
75. Vinogradov S, Fisher M, Nagarajan S. Cognitive training in schizophrenia: golden age or wild west? Biological psychiatry 2013;73:935-937.
76. Merzenich MM, Nahum M, Van Vleet TM. Neuroplasticity: introduction. Progress in brain research 2013;207:xxi-xxvi.
77. De Giglio L, De Luca F, Prosperini L, et al. A Low-Cost Cognitive Rehabilitation With a Commercial Video Game Improves Sustained Attention and Executive Functions in Multiple Sclerosis: A Pilot Study. Neurorehabilitation and neural repair 2014.
78. Bonavita S, Sacco R, Della Corte M, et al. Computer-aided cognitive rehabilitation improves cognitive performances and induces brain functional connectivity changes in relapsing remitting multiple sclerosis patients: an exploratory study. Journal of neurology 2015;262:91-100.
79. Sarkar A, Dowker A, Cohen Kadosh R. Cognitive enhancement or cognitive cost: trait-specific outcomes of brain stimulation in the case of mathematics anxiety. The Journal of neuroscience : the official journal of the Society for Neuroscience 2014;34:16605-16610.
80. Gill J, Shah-Basak PP, Hamilton R. It's the Thought That Counts: Examining the Task-dependent Effects of Transcranial Direct Current Stimulation on Executive Function. Brain stimulation 2015;8:253-259.
81. Park SH, Seo JH, Kim YH, Ko MH. Long-term effects of transcranial direct current stimulation combined with computer-assisted cognitive training in healthy older adults. Neuroreport 2014;25:122-126.
82. Science P. Available at: http://www.brainhq.com/. Accessed February 10th.
83. Krupp L. Fatigue is intrinsic to multiple sclerosis (MS) and is the most commonly reported symptom of the disease. Multiple sclerosis 2006;12:367-368.
84. Lerdal A, Celius EG, Krupp L, Dahl AA. A prospective study of patterns of fatigue in multiple sclerosis. European journal of neurology : the official journal of the European Federation of Neurological Societies 2007;14:1338-1343.
85. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques 1994;21:9-14.
86. Khan F, Amatya B, Galea M. Management of fatigue in persons with multiple sclerosis. Frontiers in neurology 2014;5:177.
87. Fernandez-Munoz JJ, Moron-Verdasco A, Cigaran-Mendez M, Munoz-Hellin E, Perez-de-Heredia-Torres M, Fernandez-de-Las-Penas C. Disability, quality of life, personality, cognitive and psychological variables associated with fatigue in patients with multiple sclerosis. Acta neurologica Scandinavica 2015.
88. Charvet LE, Serafin, D., Krupp, L.B. Fatigue in multiple sclerosis. Fatigue: Biomedicine, Healthy & Behavior 2014;2:3-13.
89. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444-1452.
90. Mills RJ, Young CA. The relation between fatigue and other clinical features of multiple sclerosis. Multiple sclerosis 2006;12:S152-S153.

91. Ghajarzadeh M, Jalilian R, Eskandari G, Sahraian MA, Azimi A, Mohammadifar M. Fatigue in multiple sclerosis: relationship with disease duration, physical disability, disease pattern, age and sex. Acta neurologica Belgica 2013;113:411-414.
92. Flachenecker P, Kumpfel T, Kallmann B, et al. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. Multiple sclerosis 2002;8:523-526.
93. Chen MY, Wang EK, Jeng YJ. Adequate sleep among adolescents is positively associated with health status and health-related behaviors. BMC public health 2006;6:59.
94. Genova HM, Rajagopalan V, Deluca J, et al. Examination of cognitive fatigue in multiple sclerosis using functional magnetic resonance imaging and diffusion tensor imaging. PloS one 2013;8:e78811.
95. Kos D, Kerckhofs E, Nagels G, D'Hooghe M B, Ilsbroukx S. Origin of fatigue in multiple sclerosis: review of the literature. Neurorehabilitation and neural repair 2008;22:91-100.
96. Braley TJ, Chervin RD. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. Sleep 2010;33:1061-1067.
97. Svenningsson A, Falk E, Celius EG, et al. Natalizumab treatment reduces fatigue in multiple sclerosis. Results from the TYNERGY trial; a study in the real life setting. PloS one 2013;8:e58643.
98. Kraft G, Bamer A, McMullen K, Amtmann D. Multiple Sclerosis Patients Taking Disease Modifying Treatments Endorse Less Severe Symptoms and Improved Quality of Life Compared with Patients Not on Treatment. Neurology 2012;78.
99. Simone IL, Ceccarelli A, Tortorella C, et al. Influence of Interferon beta treatment on quality of life in multiple sclerosis patients. Health and quality of life outcomes 2006;4:96.
100. Lange R, Volkmer M, Heesen C, Liepert J. Modafinil effects in multiple sclerosis patients with fatigue. Journal of neurology 2009;256:645-650.
101. Krupp LB, Coyle PK, Doscher C, et al. Fatigue therapy in multiple sclerosis: results of a double-blind, randomized, parallel trial of amantadine, pemoline, and placebo. Neurology 1995;45:1956-1961.
102. Branas P, Jordan R, Fry-Smith A, Burls A, Hyde C. Treatments for fatigue in multiple sclerosis: a rapid and systematic review. Health technology assessment 2000;4:1-61.
103. Asano M, Finlayson ML. Meta-analysis of three different types of fatigue management interventions for people with multiple sclerosis: exercise, education, and medication. Multiple sclerosis international 2014;2014:798285.
104. Hugos CL, Copperman LF, Fuller BE, Yadav V, Lovera J, Bourdette DN. Clinical trial of a formal group fatigue program in multiple sclerosis. Multiple sclerosis 2010;16:724-732.
105. Smith A. The Symbol Digit Modalities Test (SDMT) Symbol Digit Modalities Test: Manual.: Western Psychological Services, 1982.
106. Langdon DW, Amato MP, Boringa J, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Multiple sclerosis 2012;18:891-898.
107. Zanao TA, Moffa AH, Shiozawa P, Lotufo PA, Bensenor IM, Brunoni AR. Impact of two or less missing treatment sessions on tDCS clinical efficacy: results from a factorial, randomized, controlled trial in major depression. Neuromodulation : journal of the International Neuromodulation Society 2014;17:737-742; discussion 742.
108. Kessler SK, Turkeltaub PE, Benson JG, Hamilton RH. Differences in the experience of active and sham transcranial direct current stimulation. Brain stimulation 2012;5:155-162.
109. Kasschau M, Sherman K, Haider L, et al. A Protocol for the Use of Remotely-Supervised Transcranial Direct Current Stimulation (tDCS) in Multiple Sclerosis (MS). Journal of visualized experiments : JoVE 2015.
110. Hintze J, ed. PASS12. Kaysville, Utah: NCSS, LLC, 2013.
111. Zhang S, Paul J, Nantha-Aree M, et al. Empirical comparison of four baseline covariate adjustment methods in analysis of continuous outcomes in randomized controlled trials. Clinical epidemiology 2014;6:227-235.
112. Benedict RH, Amato MP, Boringa J, et al. Brief International Cognitive Assessment for MS (BICAMS): international standards for validation. BMC neurology 2012;12:55.
113. Razjouyan J, Gharibzadeh S, Fallah A, Khodadi A. A revisited view of the Paced Auditory Serial Addition Test (PASAT) in multiple sclerosis. The Journal of neuropsychiatry and clinical neurosciences 2010;22:451-w e438-451 e438.
114. Fisk JD, Archibald CJ. Limitations of the Paced Auditory Serial Addition Test as a measure of working memory in patients with multiple sclerosis. Journal of the International Neuropsychological Society : JINS 2001;7:363-372.

115. Parmenter BA, Shucard JL, Benedict RH, Shucard DW. Working memory deficits in multiple sclerosis: comparison between the n-back task and the Paced Auditory Serial Addition Test. Journal of the International Neuropsychological Society : JINS 2006;12:677-687.
116. Tombaugh TN. A comprehensive review of the Paced Auditory Serial Addition Test (PASAT). Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists 2006;21:53-76.
117. Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. Clin Neurophysiol 2006;117:845-850.
118. Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A. Treatment of major depression with transcranial direct current stimulation. Bipolar Disord 2006;8:203-204.
119. Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W. Modulation of cortical excitability by weak direct current stimulation--technical, safety and functional aspects. Suppl Clin Neurophysiol 2003;56:255-276.
120. Priori A. Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. Clin Neurophysiol 2003;114:589-595.
121. Antal A, Kincses TZ, Nitsche MA, Bartfai O, Paulus W. Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: direct electrophysiological evidence. Invest Ophthalmol Vis Sci 2004;45:702-707.
122. Fregni F, Thome-Souza S, Nitsche MA, Freedman SD, Valente KD, Pascual-Leone A. A controlled clinical trial of cathodal DC polarization in patients with refractory epilepsy. Epilepsia 2006;47:335-342.
123. Costa-Ribeiro A, Maux A, Bosford T, et al. Transcranial direct current stimulation associated with gait training in Parkinson's disease: A pilot randomized clinical trial. Developmental neurorehabilitation 2016:1-8.
124. Kaski D, Dominguez RO, Allum JH, Islam AF, Bronstein AM. Combining physical training with transcranial direct current stimulation to improve gait in Parkinson's disease: a pilot randomized controlled study. Clinical rehabilitation 2014;28:1115-1124.
125. Valentino F, Cosentino G, Brighina F, et al. Transcranial direct current stimulation for treatment of freezing of gait: a cross-over study. Movement disorders : official journal of the Movement Disorder Society 2014;29:1064-1069.
126. Manenti R, Brambilla M, Rosini S, et al. Time up and go task performance improves after transcranial direct current stimulation in patient affected by Parkinson's disease. Neuroscience letters 2014;580:74-77.
127. Verheyden G, Purdey J, Burnett M, Cole J, Ashburn A. Immediate effect of transcranial direct current stimulation on postural stability and functional mobility in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society 2013;28:2040-2041.
128. Benninger DH, Lomarev M, Lopez G, et al. Transcranial direct current stimulation for the treatment of Parkinson's disease. Journal of neurology, neurosurgery, and psychiatry 2010;81:1105-1111.
129. Leite J, Goncalves OF, Carvalho S. Facilitative effects of bi-hemispheric tDCS in cognitive deficits of Parkinson disease patients. Medical hypotheses 2014;82:138-140.
130. Pereira JB, Junque C, Bartres-Faz D, et al. Modulation of verbal fluency networks by transcranial direct current stimulation (tDCS) in Parkinson's disease. Brain stimulation 2013;6:16-24.