A Pilot Trial of Remotely-Supervised Transcranial Direct Current Stimulation (RS-tDCS) to Enhance Motor Learning in Progressive Multiple Sclerosis (MS)

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This is a randomized, double-blind pilot clinical trial to test a novel treatment approach to rehabilitate fine motor function in individuals living with progressive multiple sclerosis (MS) using anodal transcranial direct current stimulation (tDCS) to augment manual dexterity training. Treatment will be delivered to individuals at home using a state-of-the-art remotely-supervised telerehabilitation protocol, a major advantage for patients with respect to ease of access, feasibility, reinforcement learning, and minimal burden of in-clinic study visit participation. Improvements in fine motor skill will be assessed at each remote session using a novel portable grip device that measures execution and adaptation or learning of fingertip forces during grasp, which is more sensitive than standard measures of hand function.

Background

MS is characterized by demyelination, immune-mediated inflammation, and neurodegeneration within the central nervous system [1, 2]. MS is the most common degenerative neurologic disorder in adults of working-age [3]. 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 [3, 4]. The most common subtype of MS is relapsing-remitting and over half of these individuals transition to a progressive course; the remainder have a progressive course from the onset [5].

This study will focus on those with progressive (primary, secondary) MS subtypes. Individuals with progressive subtypes have greater disability but fewer therapeutic options (i.e., most disease modifying therapies are only available for those with the relapsing disease subtype) and are relatively underserved in the MS community. Additionally, patients with progressive MS are expected to have a stable disease course (vs. risk of relapse with relapsing MS) across the period of study.

Reduced manual dexterity occurs as a direct result of demyelination, affects more than 75% of all patients with MS, and is a leading cause of disability [6]. It is also one of the earliest markers of the disease as measures of fine motor function have been found to be more sensitive than those of either ambulation or cognitive functioning [6, 7]. The clinical manifestations of MS result from complex interactions between tissue damage, cortical reorganization and repair, and recruitment of additional neural substrates [8-10]. While decline in ambulatory function in MS corresponds with atrophy of central brain regions, decline in hand function corresponds with atrophy of both central and peripheral brain regions [11]. Hand function therefore declines with disease progression, and warrants careful assessment.

In clinical settings, the Expanded Disability Status Scale (EDSS) is used to broadly rate the level of disability from a score of 1 (no disability) to 10 (death) [12-14]. While the EDSS provides information about an individual's mobility level, it provides little information regarding hand function [15-17]. Impaired manual ability is directly correlated with pinch strength, which underlines the importance of fine motor control in the performance of even the simplest activities of daily living [18]. Consequently, even a minor reduction in hand function can compromise quality of life [19].

Rehabilitation is promising and can be completed at home. Interventions to improve and/or preserve manual dexterity are thus of critical importance in patients with MS. Although disease modifying therapies (DMT) can mitigate the progression of disability, impaired manual dexterity remains a significant problem for a majority of MS patients [20]. Rehabilitation approaches with a focus on motor learning [21], which harnesses neuroplasticity for functional recovery in MS, are promising even in patients with progressive disease [22]. For example, Tomassini and colleagues [22] found that when compared to healthy controls, although MS participants had greater levels of disability and performed more poorly at baseline, even the most disabled patients (EDSS score >4.0, many of whom had progressive forms of MS) reduce their errors through training exercises [22]. Further, after just one week of at-home training, some participants were able to achieve the same

performance levels as those of the controls at baseline [22].

Most recently, Kamm and colleagues have formalized an at-home program of manual dexterity training exercises and demonstrated that this program is superior when compared to strength-based training exercises [23]. Participants with MS (n=39) were assigned to either at-home manual dexterity or strength training (using thera-bands) for 30 minutes a day, for five days per week over 4 weeks (20 sessions). Compared to strength training, the manual dexterity training led to significant improvements on the 9-Hole Peg Test (9HPT) [24].

Transcranial direct current stimulation (tDCS) can be targeted to enhance motor learning. While promising, rehabilitation programs require intensive training for even modest effects. If the rate of motor learning could be increased, rehabilitative outcomes can be improved with greater benefit in less time – this is especially critical for patients with progressive MS to reduce the burden of accumulated disability. *Thus, we will test the central hypothesis that transcranial direct current stimulation (tDCS) paired with manual dexterity training will accelerate motor learning in patients with MS.*

tDCS is a safe, [25] therapeutic approach that utilizes low amplitude direct currents to induce changes in cortical excitability, which has shown significant effects on motor skill learning and performance [26]. More specifically, sham-controlled studies of anodal tDCS have been shown to increase the rate of motor sequence learning in healthy participants [27], and stimulation of the primary motor cortex (M1) has been shown to promote motor learning and induce both physiological and behavioral changes [28, 29].

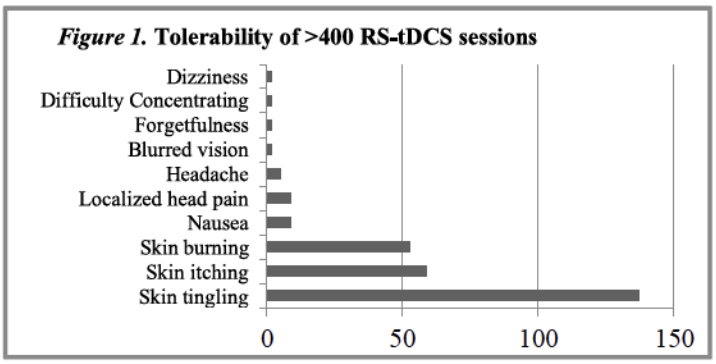
Though various non-invasive neuromodulation technologies are available, such as transcranial magnetic stimulation, tDCS has many advantages including ease of use, lower cost, and an extensive record of safety and tolerability (e.g., it has not been associated with the development of seizures). The most common side effects are specific to the electrode site and include itching, tingling, and burning. 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 [30, 31] and may be preferred to drug treatment in special populations (such as pregnant women) due to its safety advantages. tDCS is considered especially promising for enhancing the learning process in procedural training and motor rehabilitation [32]. Multiple tDCS sessions are required for optimal benefit, paired with continuous activity [33, 34]. The combined approach may increase retention and have the additional benefit of continued learning effects after treatment [35-38]. However, the approach of pairing tDCS with manual dexterity training to enhance motor learning has not yet been tested in MS.

We will employ novel and innovative approaches for treatment delivery and outcome measurement. The proposed work features two major innovations that represent significant advances from standard care and will directly translate to clinical use and establish methods for effective telerehabilitation for those living with MS:

• *tDCS and manual dexterity training will be completed at home and be remotely-supervised in real time using an innovative telerehabilitation protocol.* While the cellular mechanisms of tDCS remain to be fully understood [39], what is established is that sustained (several minutes of) tDCS can produce lasting changes in brain excitability and that these changes are cumulative with repeated sessions [40]. Repeated sessions are also necessary to produce cumulative effects as shown in neurophysiology studies and clinical trials for neuropsychiatric disorders and rehabilitation [30, 41, 42]. However, 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 routine obligations), or limited mobility and/or restricted transportation options (which can be especially burdensome for caregivers). For example, the majority of studies of tDCS use in MS have had limited conclusions due to very low sample sizes and few number of treatment sessions [41, 43-48]. Currently, the only published study to date involving the use of tDCS for motor improvement in MS included only one session of tDCS [41].

To study the multiple applications of tDCS in MS, especially when pairing stimulation with a rehabilitation program, MS participants must be able to access these treatments from home. We have established a method to pair tDCS with at-home delivery of rehabilitation for controlled clinical trials in MS. Our RS-tDCS protocol meets consensus guidelines [49], and we have validated it for remote use [50, 51]. We have also demonstrated

the ability to recruit patients rapidly for this protocol (limited only by device availability), with over 96% compliance rate for session and study completion [51]. Using remote supervision, we have administered >500 tDCS (*Fig. 1*) sessions (nearly matching the combined published experience of tDCS in MS) in participants ranging in age from 19 to 69 years and in disability from mild to severe (non-ambulatory; EDSS score 1.0 to 8.0), and including many participants with progressive disease.



• *Fine motor skill learning will be assessed using a novel instrumented portable grip device and a mobile app across the training sessions.*

Hand function in MS is most commonly measured using the 9-hole peg test (9HPT) [24], which is one of three components of the Multiple Sclerosis Functional Composite (MSFC) [24, 52-55]. The 9HPT is a timed measure of dexterity, but cannot provide detailed information about whether the impairment is in grasp execution, learning or both. The assessment of precision grasp with an instrumented grip device is a highly sensitive measure of fine motor control and motor learning in patients with neurologic impairment from stroke and MS [56-59]. It provides information about fundamental aspects of hand function such as grasp execution, adaptation of grasp to object properties, and compensatory adjustment of grasp, which may be affected to various degrees depending on the underlying CNS pathology. A schematic of the prototype device and the key variables obtained from interaction with the device are shown in *Fig. 2*:

(1) The preload phase duration (PLD) is the duration of finger contact until the onset of positive load force. It assesses the time taken to stabilize grasp and is a robust measure of grasp execution. When grasping an object, the grasping and lifting forces have to be temporally coordinated - a delay between the time to initiate grasp and the time to initiate lift compromises fine motor execution and is correlated with prolonged time taken on dexterity tasks such as the 9HPT (2). The peak load force rate (pLFR) is a measure of adaptation of fingertip forces to object weight prior to object lift. It assesses learning of the relationship between the weight of the object and the appropriate fingertip forces needed to lift it. In daily life one needs to exert the optimal amount of force to grasp objects of different weights and textures - heavier and smoother objects require faster rate of change of fingertip forces compared with lighter and rougher objects. Healthy individuals in contrast to patients with neurological disorders, learn to do so within 1-2 trials. We will examine the rate of learning of fingertip force coordination to objects of different weights with active versus sham tDCS (3) The grip force at on-lift (GFO) is the grip force applied when the object is just lifted. It assesses grip force efficiency. Typically the grip force at lift should be just enough to overcome the friction at the grip surface; however in patients with MS, the grip force is often excessively increased. In our pilot feasibility study in patients with MS, quantitative assessment of precision grasp was found to sensitively capture impairments in grasp execution and adaptation or learning of fingertip forces to object weight in high functioning patients (MS_{high}) versus low functioning patients (MS_{low}), relative to the 9HPT *(Fig. 3)*. We have now developed a portable grip

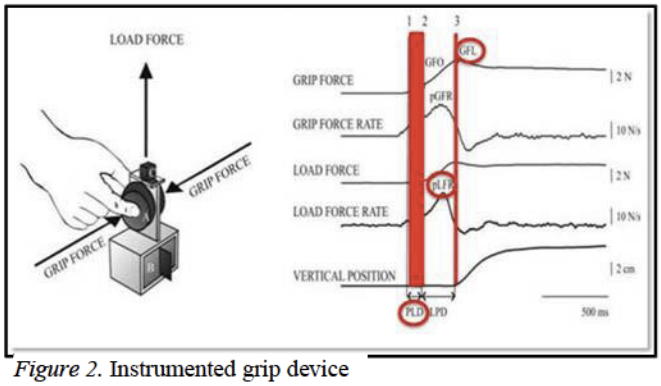


Figure 2. Instrumented grip device

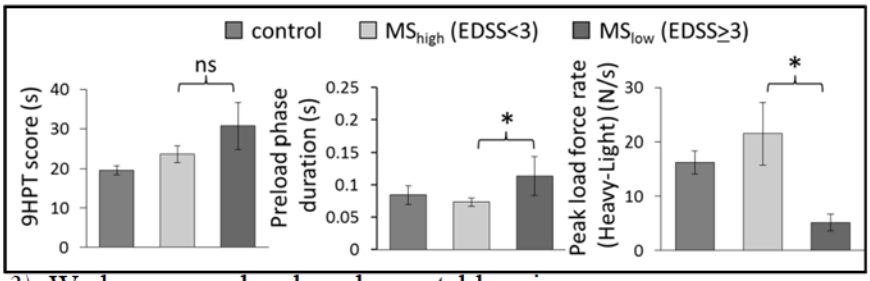


Figure 3. 9HPT scores were not different between MShigh and MSlow groups, whereas measures of grasp execution (Preload phase duration) and adaptation or learning of fingertip forces to object weight (Peak load force rate) showed significant differences

device to quantify the effect of manual dexterity training on motor learning in patients with MS using a remotely supervised telerehabilitation set up via a laptop (*Fig. 4*). The portable grip device has been validated against the grip device used in the laboratory and the data are found to be accurate and reliable.

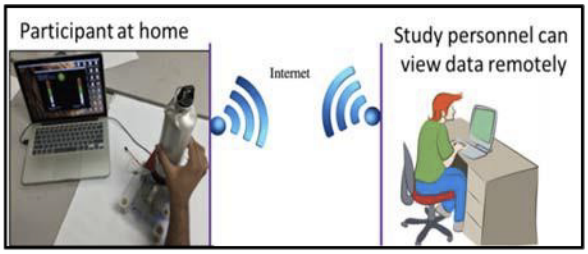


Figure 4. Portable grip device

Objective

Our objective is to test the extent to which tDCS paired with manual dexterity training improves fine motor execution and adaptation or learning to use appropriate fingertip forces according to object properties on a grasp and lift task.

Participants (n=80) with progressive MS (primary or secondary) and manual dexterity impairment (defined by slowing on the 9HPT in the dominant hand of at least 1 SD from age-based normative data) will be randomly assigned to receive 20 × 20-minute sessions of either active (up to 2.0 mA) or sham tDCS, over four weeks (Fig. 5). Enrollment criteria (Table 1) is selected to identify those who will have the ability to fully participate in the program (including device operation).

Specific Aim 1: To determine the extent to which tDCS paired with manual dexterity training improves fine motor execution on a grasp and lift task. The primary outcome will be the temporal coordination between grasping and lifting forces, as assessed by the preload phase duration (PLD).

Hypothesis 1: *We hypothesize that active vs. sham tDCS paired with manual dexterity training (provided cumulatively) will lead to improved fine motor execution as assessed by the preload phase duration during precision grasp.*

Specific Aim 2: To assess the adaptation or learning of fingertip forces to object weight when tDCS is paired with manual dexterity training. The primary outcome will be the difference in the peak load force rate (pLFR) between trials with the light versus heavy objects.

Hypothesis 2: *We hypothesize that active stimulation with tDCS vs. sham, applied to the contralateral primary motor cortex (M1-S0), will potentiate motor learning for improved dexterity in individuals living with progressive MS, as measured by adaptation or learning of fingertip forces to object weight, compared to sham tDCS.*

Active RS-tDCS (n=40) vs. Sham RS-tDCS (n=40)
+At-Home Manual Dexterity Training

- Bilateral M1-SO electrode placement [29]
- Active= anodal 2.0 mA dose × 20 minutes
- Sham= designed to ensure blinding, includes initial and ending "ramp-up/down" stimulation for 60 seconds [60]
- At-home manual dexterity training [23] paired with tDCS
- Assessment of motor learning with novel device used to measure the timing and coordination of grasping and lifting forces (before and after each daily training session) [8].

Study Feasibility and Design

Screening evaluations (*Table 2*) will include a neurological exam and medical clearance by the study physician and brief screening evaluations for ability to operate the study equipment. Baseline and follow-up (study end) assessments will include measures of manual dexterity and functioning (*Table 2*). Detailed fingertip force data during a grasp and lift task with objects of different weights will be obtained remotely at each session using the device.

Table 1. ***Inclusion/Exclusion*** **Criteria**

Inclusion:	**Exclusion:**
• Ages 18-70, right hand dominant • Definite MS diagnosis, progressive subtype [61] • 9HPT score at least 1 standard deviation below age-based normative scores [24] • Score of < 7.5 or less on the EDSS [62] (with caregiver proxy required for those with scores of 6.5 or greater)* • Ability to understand the informed consent process and provide consent to participate in the study • Negative urine pregnancy test for women of child bearing potential • 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 four-week period of training sessions with baseline and follow-up visits. • Symbol Digit Modalities Test or SDMT [63] score ≥3.0 SD from published norms	•Primary neurologic, psychiatric or other medical disorder other than MS •Use of upper extremity Botox injection within 3 months •Current use of intrathecal Baclofen •History of seizure disorder •History of head trauma in the past year or medical device in head or neck •WRAT-4[64] reading level below average (<85) (estimated general intellectual function) •Any skin disorder/sensitive near stimulation locations • 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 • History of uncontrolled or labile hypertension. • Other serious uncontrolled medical condition (e.g., cancer or acute myocardial infarction) • Alcohol or other substance use disorder • Pregnant or breastfeeding

Experimental Approach: Following our established remotely-supervised, at-home tDCS clinical trial protocol [50, 51], participants will be trained at baseline and then provided with telerehabilitation equipment to take home for study completion. The first tDCS session will be completed during the baseline visit to test tolerability and check for understanding of procedures. The tDCS protocol 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 stimulation conditions are not maintained. It reports and records a completion code for each session.

Equipment: Participants will be provided with a *1) preconfigured laptop computer; 2) a tDCS device, headgear and supply kit; 3) manual dexterity training materials; and 4) the portable instrumented grip device.* The laptop will include a program for remote access to directly provide technical support (TeamViewer [64]) and programmed to run the mobile device app for grasp device measurement. Detailed manuals of operation will be used by both the participant and study technician. Copies of patient signed documents and an instructional video will also be provided.

Mini-Clinical Trials (Mini-CT) tDCS device: For this trial, we will use equipment developed by Soterix Medical [65], a biomedical engineering company focused on providing tDCS devices to clinical trials for non-invasive neuromodulation. The mini-CT [65] (*Fig. 5*) 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. This procedure is identical for both

the sham and active condition. The device is battery-powered (rechargeable lithium ion) and operated with a user-friendly large-button keypad interface. Color-coded cables will be fused to the device, each with a corresponding electrode at the end. Each device contains monitoring and control systems that update performance and feedback over 1,000 times per second. This high sensitivity to any change in readings ensures safety while administering the treatment, and helps maintain stimulation efficacy. The device has several built-in features for

Figure 5. Device and headgear

safety and accuracy of remote administration. If there is any disruption in the correct placement of the electrodes (e.g., the headgear is moved), the device will automatically power off (gradually decreasing the current over 30 seconds). To discontinue a session at any point, the participant can press the abort "0" button to also trigger an immediate and gradual shut-off. Sessions cannot be restarted without a new unlock code. The device includes an output with easily interpreted readings that indicate the success of the stimulation after the session. When the session is successfully completed the device will generate a completion code that provides information about the session duration and quality.

Headgear: We will use custom-made headgear with the goal of simple and consistent placement according to the M1-S0 montage [66, 67]. This montage offers ease of reliable electrode placement, and wide therapeutic application [66, 68]. Based on the typical standards established across tDCS studies, we will target 2.0 mA for 20 minute sessions [66, 68]. The manual dexterity training program will be completed during stimulation. The grip device measures will be administered immediately before and after each session.

Electrodes will be securely attached to specific markings on the headset. For placement, pre-moistened one-time use sponges are attached to the headset using snap-connectors. The electrodes are then placed into the moistened sponge pockets and clipped to the headgear. The sponge pockets are provided in single-use packets, and once opened, can be readily attached in the correct placement to the headgear. A nasion marker guides accurate user placement of the headgear.

Active vs. sham programming: In this double-blind study, devices will be programmed in advance by an

Table 2. Summary of Key Measures

Administered Screening/Baseline, Study End , Extension End†
• WRAT-4[69] Reading (estimated general cognitive functioning; screening, study/extension end) • SDMT[63] (screening, study/extension end) • 9HPT[24, 70](screening, study/extension end) • Modified Moberg test of stereognosis function • Monofilament test for finger-tip pressure sensitivity • Static and dynamic 2-point discrimination tests to assess quality of fine discriminative sensation[72] • Hand grip and pinch strengths using the standard Jamar Dynamometer (Pro Med products, Atlanta, GA) • Test of Everyday Cognitive Ability (TECA) (timed instrumental activities) • PROMIS Fatigue Short-Form[74] • Positive and Negative Affect Schedule (PANAS)[75] • MS Quality of Life[76] • Timed 25-Foot Walk • Timed Up & Go (TUG)
Administered Each tDCS Session
• Device-based (*Fig. 6*) grasping and lifting forces*(pre- and post-session) • Fatigue VAS[77] • Pain VAS[78, 79] • Mood VAS[80] • Tolerability Checklist (based on commonly reported side-effects[81])
*Primary outcome; †*Those assigned to sham will be offered 10 open-label active sessions at study end*

unblinded study team member (data associate) to provide either active or sham sessions following current standards for blinding [82, 83]. During a sham session, the device is programmed to ramp up to the desired intensity (target 2.0 mA) and ramp down for the initial 60 seconds, with no current delivery during the session, and then again 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 technician will be blinded and will be asked to guess the assigned condition at study end.

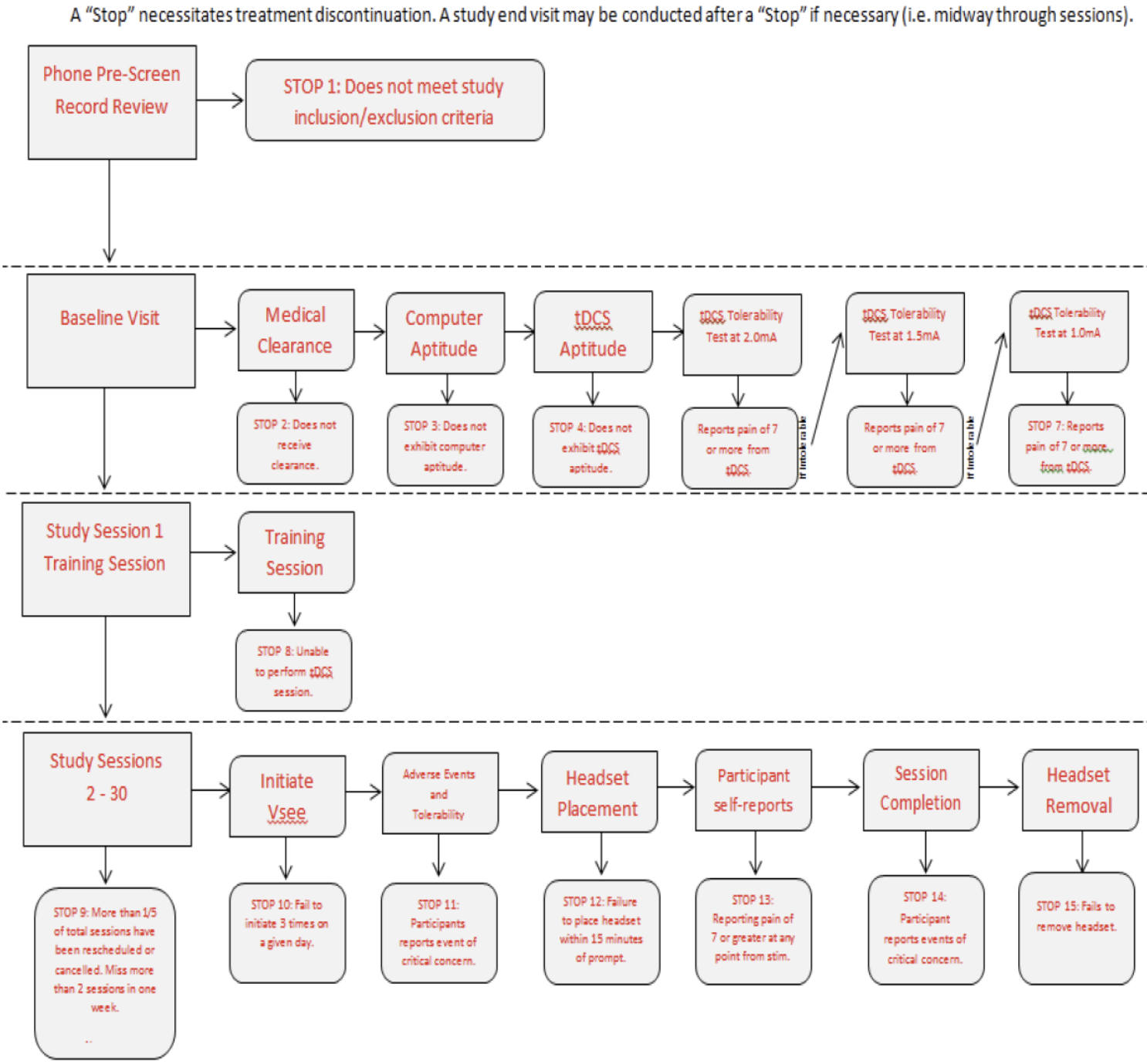
At the time of unblinding at study end, those in the sham condition will be offered to complete 10 open-label active RS-tDCS sessions while continuing the manual dexterity training program. The daily measures and an additional follow-up assessment will be collected for exploratory analyses.

***RS-tDCS session protocol*:** Participants will complete a 20 minute stimulation session supervised by a study technician through a videoconferencing platform, VSee. VSee is a HIPAA compliant teleconferencing software that encrypts data before sending, creating a secure connection between two computers. The technicians are IRB approved study team members who completed CITI, HIPAA, and study-specific training in RS-tDCS, Vsee, and Team Viewer. The technician will guide the manual dexterity training routine to be completed while during the tDCS activation (sham or active × 20 minutes) and continue for an additional 10 minutes after the device has powered off.

All remotely-supervised sessions will be completed while connected to a secure video session with the study technician. The protocol is designed to have a decision-tree series of checkpoints with "STOP" criteria that must be cleared in order to proceed at each step. These checkpoints address compliance (attendance, ability to complete the procedures as instructed, following the study guidelines) and tolerability (at any time, if any predefined events are reported, or if pain crosses a threshold of 7 or more, participation will be discontinued). For sessions 1 through 20 (and any additional optional sessions), participants in both conditions will complete brief adverse event reports before and after their sessions (with items derived from a list of the most common tDCS side-effects in previous trials [84]). In addition, participants will complete the self-report measures to address tolerability (before and after the session), pain (before, during and after the session), and brief measures of fatigue [74] and mood [75] (*Table 2*).

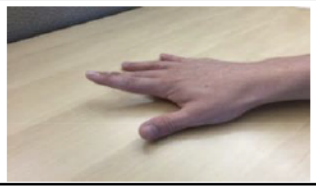
Randomization:

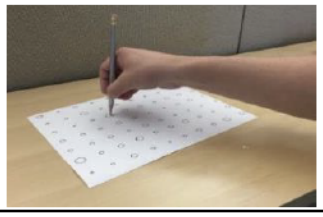
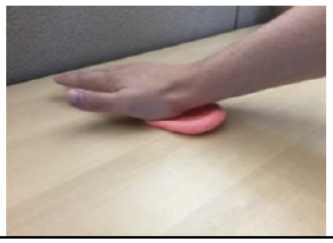
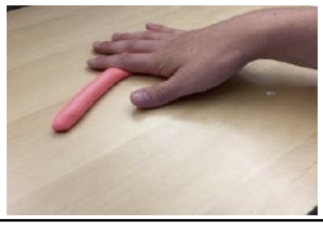
Participants will be assigned to active or sham tDCS using a stratified randomization procedure. Participants will be matched according to their degree of manual dexterity impairment (defined by slowing on the 9HPT of at least 1 SD from age-based normative data) and neurologic (motor) impairment (Expanded Disability Status Scale or EDSS score).



Clinician assessment for medical clearance may occur before or on the day of the baseline visit.

Manual dexterity training to be paired with tDCS: As above, the manual dexterity training will be based on the at-home study in MS by Kamm and colleagues (2015) [23], where the training was completed by participants in their homes and demonstrated to be superior to strength training. The training program is

Table 3. Manual Dexterity Training Program		
1.	*Finger tapping*: Participants lay their hand on a flat surface and tap their thumb against the surface twice, followed by their index finger twice and finally their middle finger twice.	

2.	*Circle completion*: Participants are given a sufficient number of circular grids for the duration of the study. Participants must carefully mark each circle with a writing utensil without letting their respective arms touch the table.	
3.	*Washer flips*: A set of washers of differing circumferences are provided to each participant. The task is simple yet demanding, as they must flip each washer. A mixture of large and small washers is to be placed upon a pre-designed grid by each participant before beginning the task to ensure the exercise is standardized from day to day.	
4.	*Bolt threading*: Participants are provided a set of nuts and bolts of differing sizes. The task is to screw the bolt on and off of a nut, three different sized nuts and bolts are provided.	
5.	*Clay Kneading*: Modeling clay of differing densities is provided for tasks 5 and 6. Task 5 requires participants to roll the clay into a ball with both hands, then to flatten the ball with the fingers of alternating hands. Participants must complete the exercise 5 times with each hand.	
6.	*Clay Shaping*: Participants roll their modeling clay into a log and use the flat side of alternating hands to create notches in the clay log. They are then instructed to briefly place their fingers several times into the newly created notches. Following completion of one repetition, the participant rolls the clay back into a log.	

completed five days per week for four weeks, for approximately 30 minutes each session, with a rotation of six upper extremity exercises. The first 20 minutes will be paired with the tDCS session (active or sham), and then training will continue for an additional 10 minutes after the stimulation to maximize learning potentiation [29].The simple tasks are each designed to be scalable to provide a challenge to patients across a range of functioning levels. The simple training materials (*Table 3*) include nuts and bolts, a set of varied sized washers, and a set of modeling clay of differing densities. The study technician will be in live contact with the participant throughout the duration of the session. Additionally, a manual is provided with intricate details of each of the exercises, to advise participants should they have questions before beginning a session.

Assessment of grasp (Primary Outcomes): Before and after each manual dexterity training session (with active or sham stimulation), the portable instrumented grip device will be used to assess grasp execution and learning. This will enable measurement of improvement in fine motor execution and rate of motor learning throughout the duration of the study. In this manner, we will measure both pre- and post-treatment changes as well as cumulative changes across the daily sessions. This will provide a robust data set to examine learning of fine motor control in patients with progressive MS. The portable grip device consists of a square platform on which a load-cell fitted with a strain gauge is mounted. The other end of the load-cell contains a 3D printed circular coaster and plates forming a

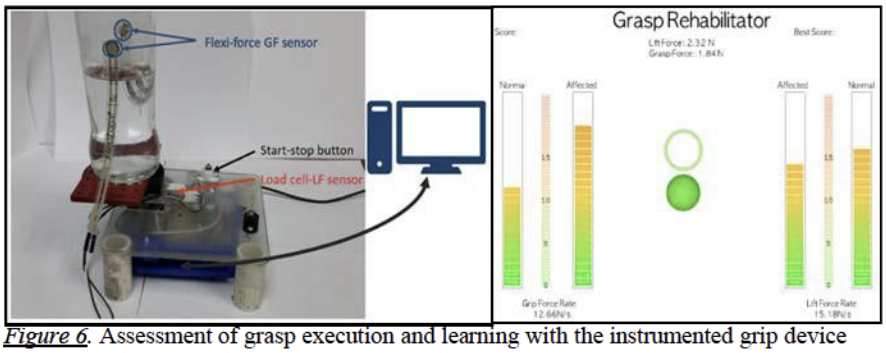


Figure 6. Assessment of grasp execution and learning with the instrumented grip device and app

platform where objects can be placed to measure load force (Fig. 6). The sensitivity of the load force sensor is 1g, i.e. 0.001N. The grip force measurement sensors use two 9.53mm diameter flexi-force sensors from Tekscan connected with a low-power linear amplifier. The sensitivity of the grip force sensors is 5g, i.e. 0.05N. The grip forces obtained from the two sensors are averaged to yield the grip force. The filtered load force and grip force data are directly differentiated over a 10ms window to obtain the load force and grip force rates. Data are sampled with a 10-bit analog to digital converter (ADC) available on the Arduino micro microcontroller. The device is fitted with a start-stop button to begin data collection. The implementation of flexi-force sensors to measure grip force provides versatility of using real-life objects such as a can, jar, glass, or bottle of various weights to be used as test objects. Four test objects of known weights, between 50g and 600g (as the load force sensor has been calibrated across these weights) will be used as "light" and "heavy" objects. The grip force sensors will be placed on a finger-tip interface that will be attached to the fingers to enable a constant grip surface when grasping the various test objects of different weights.

Instructed by the study technician, participants will press the start-stop button once to begin data collection. They will reach and grasp the test object (of known weight) placed on the coaster using their thumb and index finger, lift it approximately 5 cm from the coaster, and hold it for approximately 3 seconds before bringing it back down on the coaster. Each day, participants will complete two sets of ten lifts before and after the stimulation session and the sets will have designated weights and textures allocated to them based on a randomized schedule. The timing and amplitude of the grip and load forces and force rates will provide measures of grasp execution and learning of fingertip forces as shown in Fig. 6.

Database and Patient Information

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

Additional Quality Assurance Measures

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

Data Safety Monitoring Plan

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 will be assessed by tDCS technician at every session; measured before, during and after each session. Treating physicians will monitor and assess the relevant AEs and serious AEs in the study chart and will treat participants with AEs appropriately, per usual care. AEs will be collected from the start of the study until a participant terminates from the study; those that are unresolved at the time of termination will be followed until they resolve or up to 30 days. 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. All adverse events will be reported to IRB per NYU policy and to DoD via Quarterly Technical Progress Report.

We will submit study data safety monitoring reports to the IRB after 10 participants are enrolled in the active condition (approximately 20 total participants between active and sham condition), and follow with reports after the enrollment of the 40th, 60th, and 80th participant.

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, adverse and/or serious events 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). 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.

Independent Research Monitor

Lana Zhovtis Ryerson, MD will serve as the independent research monitor appointed to the study. The independent research monitor, is an independent expert commissioned and charged with the responsibility of evaluating cumulative safety and other clinical trial data at regular intervals. As such, the primary objective of the independent research monitor is to monitor the safety of the subjects enrolled and to be enrolled in the Study by reviewing the available clinical data at scheduled time points, as well as on an ad hoc basis, as needed.

After the review of each Data Safety Monitoring Report, which will be generated after enrollment of the first ten active condition participants and after the 40th, 60th and 80th participant, the independent research monitor will provide the official recommendation to the PI regarding the appropriateness of continuing the study, from a safety perspective, as well as any other recommendations relevant to study conduct and/or patient safety.

The independent research monitor is authorized and charged to perform the following functions:

- Provide timely review and approval of, and operate in accordance with the specifications outlined in the protocol.
- Review the provided study documents that are approved by the PI for review such as the protocol.
- The independent research monitor will review study data to ensure the safety of subjects enrolled in the study and make recommendations concerning study conduct.
- The independent research monitor may, contact and involve outside expert consultants who may provide additional, relevant insight or expertise, regarding any specific issues that may arise (once they have entered into confidentiality disclosure agreements). Outside expert consultants should not be exposed to confidential, unblinded data unless absolutely necessary for the consultant's input to be meaningful.
- Provide timely response to requested review of documentation and meeting availability requests made to independent research monitor.
- Attend the Kick-Off meeting to receive training, protocol orientation and research monitor operational training.
- Monitor the safety of patients enrolled and to be enrolled in the Study through scheduled review of accumulating clinical data from the ongoing clinical trial.
- Review and evaluate the content of all Data Safety Monitoring Reports received.
- Ensure that blinded representatives (specifically including the independent research monitor), and Study representatives are not exposed to the confidential, unblinded data made available to the independent research monitor. The Unblinded personnel has the same access to the data that is reviewed by the independent research monitor; therefore, it is not necessary for the independent research monitor to take steps to maintain this individual in a blinded position.
- Maintain ultimate responsibility for safe study conduct, according to ICH Good Clinical Practices (GCP) Guideline.

The Research Monitor is responsible to oversee the safety of the research subjects and report observations/findings to the IRB or a designated institutional official. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

Potential Risks & Benefits:

tDCS:

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 technique that is considered effective in modulating brain excitability in a manner that may support learning and with adverse events (different than sham) limited to tingling, itching, and redness that dispel after stimulation stops. In a prior study of use in a vulnerable population (developmentally disabled children), the FDA issued a NSR for tDCS device (see attached letter). The letter provided as an example of the FDA's designation of tDCS devices as having abbreviated-IDE. Because of its prior designation of tDCS devices as abbreviated-IDE, trials do not typically seek further declaration. In the letter provided, Dr. Wasserman specifically sought FDA review of the trial due to the use of tDCS in a vulnerable population (developmentally disabled children). To date, hundreds of trials have been designated as non-significant-risk by IRB review which provides its abbreviated IDE status. Results of completed trials, including our own work in MS using this protocol, have supported the risk designation provided by IRBs. The Stony Brook Medicine IRB confirmed the NSR and abbreviated IDE status of tDCS for our study.

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

Hand held grip device:

The grasping and lifting tasks carry no risks beyond those of ordinary activities. Patients will be allowed to take frequent rest breaks during the sessions. There may be other risks or discomforts in the study that we don't know about.

The cup controller, novel physical object game controller consisting of a plastic cup exterior 5 inches tall and 2.75 inches in diameter. The cup is instrumented with an ADXL- 345,3-axis accelerometer (Analog Device Inc. Norwood, MA) to detect object orientation and FSR 406 (Interlink Electronics Camarillo, CA) force sensors to detect user grip force. An Arduino Uno R3 using an ATmega328 Microcontroller (Atmel San Jose, CA) is used to record and integrate sensor data. The cup game controller will be compared with a standard Logitech optical mouse and with a Nintendo Wii controller.

Loss of Confidentiality:
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 administering the grip lifts 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 not receive any direct benefits from participating in this research study. We hope the knowledge gained from this study will help others with MS in the future.

Payment for participation:
Participants will receive up to $100 in total compensation. They will be compensated $50 for the initial screening and baseline visit, and $50 for the end of study 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.

In order for participants to receive a payment check or gift card, they will need to provide the study staff either their Social Security number or Alien Registration number. If participant does not have either of these numbers, participant may be enrolled in the study but will not receive any payment.

Power Analysis and Data Analysis Plan

Sample Size Determination: We calculate our sample size for the primary outcomes, □preload phase duration and □peak load force rate across light and heavy weights from pre- to post-treatment. Based on our preliminary data, these variables are approximately normally distributed with small variance. Expecting a medium effect size (0.5) for the difference in □preload phase duration between the active tDCS and the sham tDCS groups, group size of 30 in each arm (total 60) will achieve 80% power to detect the effect size of 0.5 with a significance level of 0.05 using a two-sided t-test. A similar effect size is expected for the □peak load force rate. Accounting for 25% attrition of the sample, the actual sample size will be 40 in each arm (total 80).

Data Analysis Plan: For Specific Aim 1, to determine the extent to which tDCS paired with manual dexterity training improves fine motor execution on a grasp and lift task, the primary outcome will be the temporal coordination between grasping and lifting forces, as assessed by the preload phase duration with active tDCS compared to sham tDCS. To test our hypothesis that active vs. sham tDCS will significantly reduce the preload phase duration pre- to post-intervention with active compared with sham-tDCS paired with training, we will perform a repeated measure ANOVA for the two groups from pre-to-post-intervention on the preload phase duration which is the primary outcome measure for grasp execution. For each group, the effect size will be estimated and reported with mean and 95% confidence intervals. *We expect that the impairment in grasp execution will be significantly reduced with active tDCS versus sham tDCS from pre- to post-treatment.* Secondarily, the change in pre-load phase duration will be correlated with the change in timing on the 9HPT as well as in manual dexterity scores in the two groups.

For Specific Aim 2, to assess the adaptation or learning of fingertip forces to object weight when tDCS is paired with manual dexterity training. The primary outcome will be the difference in the peak load force rate between trials with the light versus heavy objects. To test our hypothesis that active vs. sham tDCS paired with training will optimize the difference in the peak load force rates between the light and heavy objects pre- to post-intervention, we will first compare participants' performances to that of healthy controls. A normative database for the optimal peak load force rate for healthy controls in a population already exists [85]. Using the existing database as a benchmark we will perform a repeated measure ANOVA for the two groups from pre-to- post-intervention. For each group, the effect size will be estimated and reported with mean and 95% confidence intervals. *We expect that the impairment in grasp adaptation or learning will be closer to the benchmark with active tDCS versus sham tDCS from pre- to post-treatment.* One of the significant contributions of this proposed study is that we will be able to track detailed recovery progression for both treatment groups over the 20 sessions. We will use longitudinal growth curve modeling [86] to delineate typical types of recovery trajectories in each group. We will assess the relationship between within-session and between-session learning

trajectories to deepen our understanding on how short-term learning affects the longer-term treatment response.

Transition Plan

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. Even relatively minor reductions in manual dexterity can lead to major problems in daily life, and this is a leading cause of MS-related disability. Combining tDCS with manual dexterity training accessed from home represents a major advance that is immediately applicable to real-world clinic use. In sum, this study represents a timely and much-needed advance for both the study of tDCS in general, and for the rehabilitation of manual dexterity impairments in MS specifically, through the use of a telerehabilitation approach.

The remotely-supervised methods to be piloted can transform tDCS into a viable treatment modality. The study's protocol is highly generalizable for use in clinical trials to evaluate other areas of potential efficacy for tDCS (including cognitive impairment, mood disturbance, pain and sleep problems) in MS as well as in many other conditions. To date, the use of tDCS has largely remained within the research realm with few treatment sessions studied in small sample sizes. However, technology is rapidly advancing with the emerging development of devices marketed directly to the consumer without any clinical study. In this context, it is particularly critical to facilitate research that will determine the use of the technology that will safely lead to the greatest benefit. Our innovative protocol will facilitate study enrollment and much more extensive study of the cumulative treatment effects.

This trial will be a definitive step towards determining the treatment benefit of tDCS for enhancing motor rehabilitation. Applying preliminary findings for use in MS, we will directly measure the cumulative treatment effect of pairing tDCS with a program of rehabilitation. In addition, our novel measurement device will allow for a better understanding of the relation of grasp and grip learning to other measures and in response to training exercises. The direct next step from this pilot study will be a definitive trial utilizing our remotely- supervised protocol to improve manual dexterity.

Data Sharing Plan

The data derived from this project will be published in peer-reviewed scientific publications and presentations. In order to cater to the interests of a broad spectrum of audience, different aspects of the proposal will be published in corresponding specialized journals and symposia. Special attention will be taken in preparing the manuscripts to include details of materials and methods including protocols, analytical tools, and supporting data for the characterization of compounds. The data will be also presented through lectures and research seminars.

As soon as the final data is accepted for publication, the data will be shared with interested researchers through personal communications. Whenever possible, we will also deposit data in public archives, web sites, and data centers after achieving the milestones of this grant application. Thus, data will be made available to the public and research communities in a timely format, amenable to further research and development. This will ensure other scientists pursuing the topics in further directions and support testing of new or alternative hypotheses and methods of analysis. For researchers interested in additional methodological details of our work or in comparing their own data to our findings, we will provide a database for anonymized data/image download. Any clinical data will be anonymized and only related through participant codes so that data can be shared in a HIPAA-compliant manner.

Ethical Considerations

The goal to alleviate debilitating fatigue is the major ethical driver for this study. A first concern is whether the tDCS may cause any effect that would be considered harmful. As described, across hundreds of clinical trials, including in MS and our pilot studies, tDCS has been found to be safe and well-tolerated [30, 87, 88]. A recent and comprehensive safety review found no risk of adverse events with tDCS as planned for use in this study [25]. All potential participants will be warned of any possible side effect. Prior to enrollment, participants will undergo medical clearance with a confirmation of enrollment criteria including cognitive screening measures to ensure that they have sufficient cognitive capacity to understand the fundamental principles of clinical research, the specifics of this study, and to comply with study procedures.

Dr. Charvet's focus of her career has been to measure and ameliorate the symptoms of Multiple Sclerosis including cognitive impairment and fatigue. She is a world leader in remote-supervised transcranial direct current stimuliation (RS-tDCS) including several publications on safety and feasibility. She brings over 20 years of clinical research experience to this project, including key investigator roles in past NIH-supported projects. She is a licensed clinical neuropsychologist and training has included the completion of an ABPP-ABCN certified internship and postdoctoral fellowship programs in clinical neuropsychology with both adult and pediatric training.

Dr. Krupp's qualifications include over a 25 year record of clinical and research experience on multiple sclerosis (MS), a publication history covering cognitive function and related aspects of the disease, leadership experience directing observational studies on cognition in MS, NIH supported multicenter trials on fatigue and cognition, and access to a large group of patients with MS.

Dr. Preeti Raghavan is an expert in motor learning after neurological injury, particularly re-learning of manual dexterity. She developed the instrumented grip device in conjunction with the computer interface and training algorithms for in-home use.

Dr. Marom Bikson (collaborator) is an international leader in the field of tDCS for clinical trials, and will provide his expertise in trial design and execution, as well as serve as a liaison for the medical device company Soterix. He will guide the research regarding the mechanisms of action of tDCS incorporating neuroimaging data and electrode placement[23].

Dr. Ying Lu, is an expert in statistical methodology for model selection and hypothesis testing for high dimensional biomechanical data from the Center for the Promotion of Research Involving Statistical Methodology (PRISM), at NYU Steinhardt.

No additional DoD trainings are required.

Once enrolled, all participants (including their caregiver or other proxy as warranted) will be trained to operate study equipment by use of established training protocols that include screens for aptitude and extensive safety checks at each step. All sessions will be administered with real-time supervision to monitor the participant's status (related to safety or tolerability) or wish to discontinue during office hours and staff availability. These measures prevent any participant from continuing if there are any adverse effects, improper use of the device or study equipment, or issue related to compliance. Procedures are in place to immediately alert the study neurologist if any potentially adverse events are reported.

While the overwhelming majority of tDCS trials to date have found only beneficial results, two recent studies have reported possible suppression of cognitive performance after the administration of one tDCS session [89, 90]. These findings are questionable given the extensive and well-documented improvements in cognition and learning with tDCS application [66, 68], and one session is not likely to have a sustained effect (positive or negative) [30]. Further, there is no indication of any post-session decline or cognitive changes in our feasibility study. While we did not include cognitive measurement at each session, participants' mood improved after each treatment (increased positive affect, $p=0.07$; decreased negative affect, $p=0.04$).

Additionally, participants had no indication of cognitive decline following the treatments, with scores on the SDMT (a representative measure of cognitive functioning in MS[91],[92]) slightly improving after ten sessions (44.9 ± 13.5 vs. 46.6 ± 15.4, $p=0.28$).

A second possible concern is that participants may not receive expected benefit. In this case, the study design and randomization procedures will be explained in detail to all participants. Those in the sham condition will be offered to continue with 10 open-label sessions at study end which may provide them with treatment benefit. At study completion, all participants will receive feedback on their study outcomes and those that do not experience any benefit with active treatment may gain direction for future trials of tDCS that may be

adapted to their individual needs based on the results of this study.

SUBJECT RECRUITMENT AND CONSENT/ASSENT:

Method of Subject Identification and Recruitment

Research candidates will be recruited from the NYU MS Comprehensive Care Center patient database as well as from non-NYU referring facilities and/or physicians. 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.

Participant personal information will be kept in Ripple™, a secure web application designed for the storing and management of personally identifying information of research participants. Ripple was initially developed at the University of Michigan to provide a user friendly, web-based secure interface where research teams can centralize the storage and management of research participants' personal information, including name, participant ID, demographics, and study workflow (e.g., appointments). Participant information managed with Ripple™ is private and secure. This information is kept in fully encrypted format inside dedicated databases that are segregated from other Ripple™ accounts and thus only authorized study staff will have access to the study data. Likewise, Ripple infrastructure complies with the privacy and security guidelines of the Health Insurance Portability and Accountability Act (HIPAA), including 2048-bit data encryption in transit and at rest, automatic logoff, audit trail, daily backups in triplicate dedicated servers, firewall, custom access permission for lab members, zxcvbn password strength estimation, and enterprise administrative safeguards to prevent unauthorized staff from accessing participant information. Furthermore, Ripple™ is used only for storing personally identifiable information of participants and is not used to capture other research data (e.g., questionnaires, health records, etc.). This ensures that the personally identifiable information and research data are segregated. Ripple™ is already being used at NYU Langone Health.

Informed Consent Process

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.

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, Dr. Charvet or Dr. Raghavan will assess 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 an IRB study representative 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.

Informed consent can be obtained on paper documents or electronically via REDCap. There is no difference between the paper and electronic versions. Participants who are on-site and prefer an e-ICF (electronic informed consent form) will be presented with the e-ICF by a study team member on a tablet or other device to complete via REDCap. Participants will sign electronically using a mouse, finger, or stylus and have the option to receive a copy via e-mail.

Remote participants will be e-mailed a secure REDCap link to access, review, and sign the ICF and participant agreement. A study team member will contact the participant on the phone to review the consent form together, answer any questions, and provide technical assistance if necessary. The study team member will confirm that the participant is in a private room to ensure confidentiality. Participants will have the option to navigate forward and backward and can stop the consent and resume at a later time. Participants will be able to contact a study team member should they have additional questions before signing.

The e-ICF can be signed electronically using a mouse, stylus or finger. Once completed, the e-ICF will be saved to REDCap and the participant can download a signed copy or have it e-mailed.

Subject Capacity

All participants will be confirmed to have the capacity to provide consent by Dr. Charvet 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. Patients will be allowed ample time to review the consent form and ask questions in a private room.

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. An enrollment note will be kept with the original ICF as documentation confirming the ICF process.

Costs to the Subject

There will be no cost to the participants.

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