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Transcranial Direct Current Stimulation Is Feasible for Remotely Supervised Home Delivery in Multiple Sclerosis

Margaret Kasschau, BS*; Jesse Reisner, BS†; Kathleen Sherman, MS*; Marom Bikson, PhD‡; Abhishek Datta, PhD§; Leigh E. Charvet, PhD*

Objectives: Transcranial direct current stimulation (tDCS) has potential clinical application for symptomatic management in multiple sclerosis (MS). Repeated sessions are necessary in order to adequately evaluate a therapeutic effect. However, it is not feasible for many individuals with MS to visit clinic for treatment on a daily basis, and clinic delivery is also associated with substantial cost. We developed a research protocol to remotely supervise self- or proxy-administration for home delivery of tDCS using specially designed equipment and a telemedicine platform.

Materials and Methods: We targeted ten treatment sessions across two weeks. Twenty participants ($n = 20$) diagnosed with MS (any subtype), ages 30 to 69 years with a range of disability (Expanded Disability Status Scale or EDSS scores of 1.0 to 8.0) were enrolled to test the feasibility of the remotely supervised protocol.

Results: Protocol adherence exceeded what has been observed in studies with clinic-based treatment delivery, with all but one participant (95%) completing at least eight of the ten sessions. Across a total of 192 supervised treatment sessions, no session required discontinuation and no adverse events were reported. The most common side effects were itching/tingling at the electrode site.

Conclusions: This remotely supervised tDCS protocol provides a method for safe and reliable delivery of tDCS for clinical studies in MS and expands patient access to tDCS.

Keywords: Feasibility, multiple sclerosis, remotely supervised, tDCS, telemedicine

Conflict of Interest: CUNY has patents with Marom Bikson as inventor. Marom Bikson is an advisor for and has equity in Soterix Medical. CUNY has patents with Abhishek Datta as inventor. Abhishek Datta is an employee and has equity in Soterix Medical.

INTRODUCTION

Multiple sclerosis (MS) is the most common neurological disorder among adults of working age (1), and is associated with tremendous cost in terms of both economic viability and quality of life. 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). It is frequently accompanied by a range of symptoms that do not have optimal options for management, such as cognitive difficulties, fatigue, mood, sleep disturbances, pain, and sensory and motor impairments.

Transcranial direct current stimulation (tDCS) refers to the use of low amplitude direct current to induce changes in cortical excitability. In comparison to other approaches to noninvasive brain stimulation, it is relatively low-cost to administer and the devices are portable. Across an extensive and variable body of clinical studies, tDCS has been found to be consistently safe and well-tolerated (5–7). It has also been associated with a wide range of symptomatic benefits that are potentially relevant for those living with MS (8–30).

Initial studies of tDCS in MS have found preliminary signals for efficacy in targeting symptoms of fatigue (15,23,25), sensory deficits and pain (13,21), motor problems (24), and cognitive impairment (30). However, these initial studies have included relatively small samples and few active treatment sessions. Definitive clinical trials are needed to provide the parameters needed to transition to clinical implementation.

In addition to larger sample sizes, it is important to study tDCS administered across multiple treatment sessions in order to evaluate its clinical benefit. The effects of tDCS are cumulative, with little expected lasting change or benefit following only one application, the amount often studied in MS (20,24). Instead, investigators in other conditions have found optimal benefit after 20 sessions or

Address Correspondence to: Leigh E. Charvet, Department of Neurology, New York University School of Medicine, New York, NY, USA. Email: leigh.charvet@nyumc.org

* Department of Neurology, New York University School of Medicine, New York, NY, USA;
† Arizona College of Osteopathic Medicine, Glendale, AZ, USA;
‡ Department of Biomedical Engineering, The City College of New York of CUNY, New York, NY, USA; and
§ Soterix Medical Inc., New York, NY, USA

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Table 1. Eligibility Criteria.

Inclusion Criteria	Exclusion Criteria
• Ages 18-70 • Definite MS diagnosis, all subtypes [95] • MS-related changes in cognitive functioning • A score of 6.5 or less on 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, ~150 kbps, 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 participate in the study	• Visual, auditory and motor deficits that would prevent full ability to understand study instructions or operate the tDCS device or study laptop, as judged by treating 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 • Current 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) 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

more [e.g., depression (11)]. Multiple administrations are also important when pairing tDCS with rehabilitation to enhance program outcomes (30).

Trial designs with consecutive repeated tDCS sessions, potentially spanning weeks or months, present an obstacle for access for many living with MS. Daily travel to a treatment facility is not feasible for most individuals with MS, who often have a full work and family schedule, limited mobility and/or restricted transportation options. However, the alternative of self-directed home use, where a participant is simply given a tDCS device to self-administer treatments on their own, is not safe or feasible. Safety concerns include the overall absence of clinical supervision and the potential for misuse of an ungoverned device. Further, in the context of a clinical study, the stimulation would not be standardized or reproducible.

To provide accessible treatment while maintaining clinical trial standards for study in MS, we have developed a remotely supervised tDCS protocol. A telemedicine protocol featuring closely supervised, remotely delivered tDCS represents an effective method by which to circumvent these logistical barriers.

Our protocol was developed following our group's experience with home delivery of a cognitive remediation program in MS (31). The design meets collaborative guidelines and standards for remotely supervised tDCS that were established through a working group of diverse tDCS clinical investigators (32,33). Administration is via a videoconference using an extensive procedure that includes safety and tolerability stops throughout, specially designed headsets for use in MS, and a device that has been developed to allow stimulation to be governed by the supervising study technician. To date, at-home tDCS has been studied in combination with occupational therapy following stroke (34), and a trial design has been proposed for self-administration in neuropathic pain following positive response to transcranial magnetic stimulation (TMS) (35). Here we report the details of our protocol and initial feasibility, safety and tolerability data from a sample of MS participants.

METHODS

Ethics Statement

Stony Brook University Institutional Review Board (IRB) approved this protocol on February 10, 2015 (2014-2877-F).

Participants

All participants were recruited through the Stony Brook Medicine MS Comprehensive Care Center. Prior to the baseline visit, all enrolled participants were given medical clearance by a study physician to ensure that no conditions contraindicated for tDCS treatment were observed. The full list of inclusion/exclusion criteria specific to the requirements of a remotely administered tDCS can be found in Table 1.

Participants were told only that the methods were in development for future study, and were not enrolled for any specific therapeutic use of tDCS. Participants who did not have sufficient manual dexterity (e.g., Expanded Disability Status Scale or EDSS (36) score of 6.5 or greater) were offered the option to participate along with a caregiver proxy who could assist with tDCS headset placement and device operation (also required to complete all training procedures together with the participant).

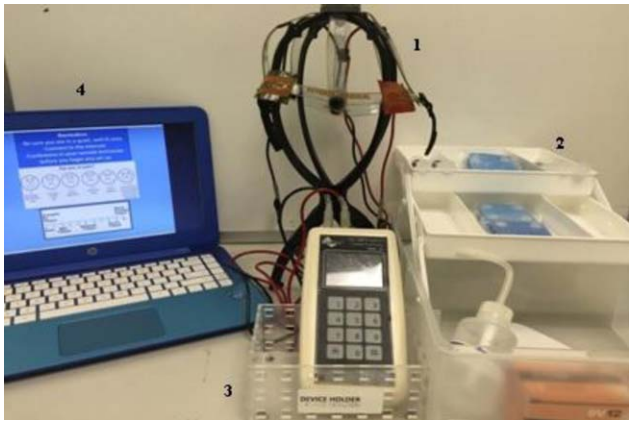

Figure 1. Participant study materials. 1) Headstrap with cap-like design; 2) Device kit with materials labeled for daily use; 3) Mini-CT device with large, easy-to-use response pad; 4) Study laptop configured with VSee, TeamViewer, and daily assessment scales.

Study Equipment

For this study we used the tDCS mini-Clinical Trial (CT) device (37). The tDCS device functions by delivering direct electrical current through sponge electrodes (5cm x 5cm) that contact the skin of the forehead. The unit only "unlocks" one dose per code, controlled by a study technician. The device was pre-programmed to deliver 20 minutes of 1.5 mA stimulation during each session. The sham option was not used in this study and all sessions were active.

Headset design is critical for at-home administration as streamlined and simplified procedures are necessary to facilitate successful self- or proxy-placement and to provide reliable and standardized electrode positioning (33). In collaboration with Soterix Medical, the accompanying head strap (EASYstrap) was customized to be used for the MS patient population. Several design iterations led to fixed position loading and clear labeling for reliable electrode placement (anode and cathode). This configuration provided a uniform bilateral dorsolateral prefrontal cortex (left anodal) montage, centered using a nasion marker with the guidance of the study technician. The easily placed DLPFC montage has been extensively optimized (38) and offers wide therapeutic applications for targeting the key symptoms for potential therapeutic benefit in MS [e.g., targeting cognitive functioning (39) and fatigue (40)].

To minimize the variability in electrode setup, we pre-filled syringes with 6mL of saline solution (which is the optimal retention capacity that was quantified in advance) and instructed participants to use one per day per sponge (i.e., two syringes per day), moistening both sides evenly. The contact was ensured by the headgear which is designed to provide a consistent and controlled amount of pressure.

Participants were provided with a home tDCS kit (Fig. 1) and study laptop. The home tDCS kit included the head strap, sponge pockets, the pre-loaded saline syringes labeled by day, a spare wash bottle of saline, spare 9V batteries, and a device holder. The study laptop included a mouse (with an adaptive mouse for those with motor impairment). Study laptops were configured to include visual analog scales for pain and fatigue, as well as a readily accessible document containing the list of potential side effects to be reviewed each day with the study technician. In addition, VSee (41), a telemedicine software was used to web conference with participants. Participants were provided with a unique VSee user ID linked to each individual laptop. Participants were not provided with the password, and if log-out accidently occurred, the study technician completed log-in. Laptops were also programmed with TeamViewer (42) software, which allowed technicians to gain remote access to the participant's desktop. In addition, participants were required to have a mobile or cellular phone at their workstation. The study technician established access to a viable phone connection in advance of each session to provide a backup method of communication in case of any loss of network connection.

The use of TeamViewer minimized the amount of technical set-up required by the participant. As long as the participant was able to open the study laptop and was connected to Wi-Fi, the study technician could remotely configure the cognitive training games, open visual analog scales and tolerability reports, and initiate web conference.

Study Procedures

The home sessions were remotely supervised in real-time, following a detailed set of "stop" criteria (Fig. 2). To start each session, the mini-CT impedance reading was provided to the study technician via the videoconference feature. Unlock codes were only given if impedance readings were moderate or optimal. In addition, each mini-CT device contains monitoring and control systems that update performance and feedback $>$1000 times per second. If there is any disruption in the correct placement of the headstrap or electrodes, in addition to the change in the visual display, the device beeps (audio alert) to notify of atypical resistance condition leading to a pause event. The device will automatically power off (gradually decreasing the current more than 30 seconds).

During the 20-minute stimulation period, participants completed web-based adaptive cognitive training games to pilot procedures to combine remotely supervised tDCS with rehabilitation. Designed and customized for research, this research program includes a set of classic attention, processing and working memory exercises through a platform designed by Lumos Labs (43). We selected this platform for ease of administration and high compliance rates among our MS participants (31).

Table 2 shows the study measures included as clinical outcomes. Cognitive assessment (44,45) and symptom inventories (46–48) were administered at baseline and study end. In addition, daily measures of pre- and post-session tolerability (49), pain (50,51), fatigue (52), and mood (53) were administered. A pain inventory was also taken mid-session as well (Table 2).

Baseline Training and Session 1

After screening, participants (or proxy) were trained in tDCS procedures and completed the initial baseline visit in clinic, which included a tDCS tolerability test and initial tDCS session. If the participant required a proxy (i.e., family caregiver or aide), the proxy had to pass a capacity screening together with the participant and receive the same structured training.

Home Visit and Session 2

The next day, a study technician visited the participant in their home to deliver study equipment and oversee the first virtual session. Participants alone or in partnership with their proxy were instructed to complete the tDCS administration independently while connected to a study technician in the lab using the VSee platform.

Remote Sessions 3–10

Study technicians were fully trained on the use of the device, which included device programming, unlocking tDCS doses, and

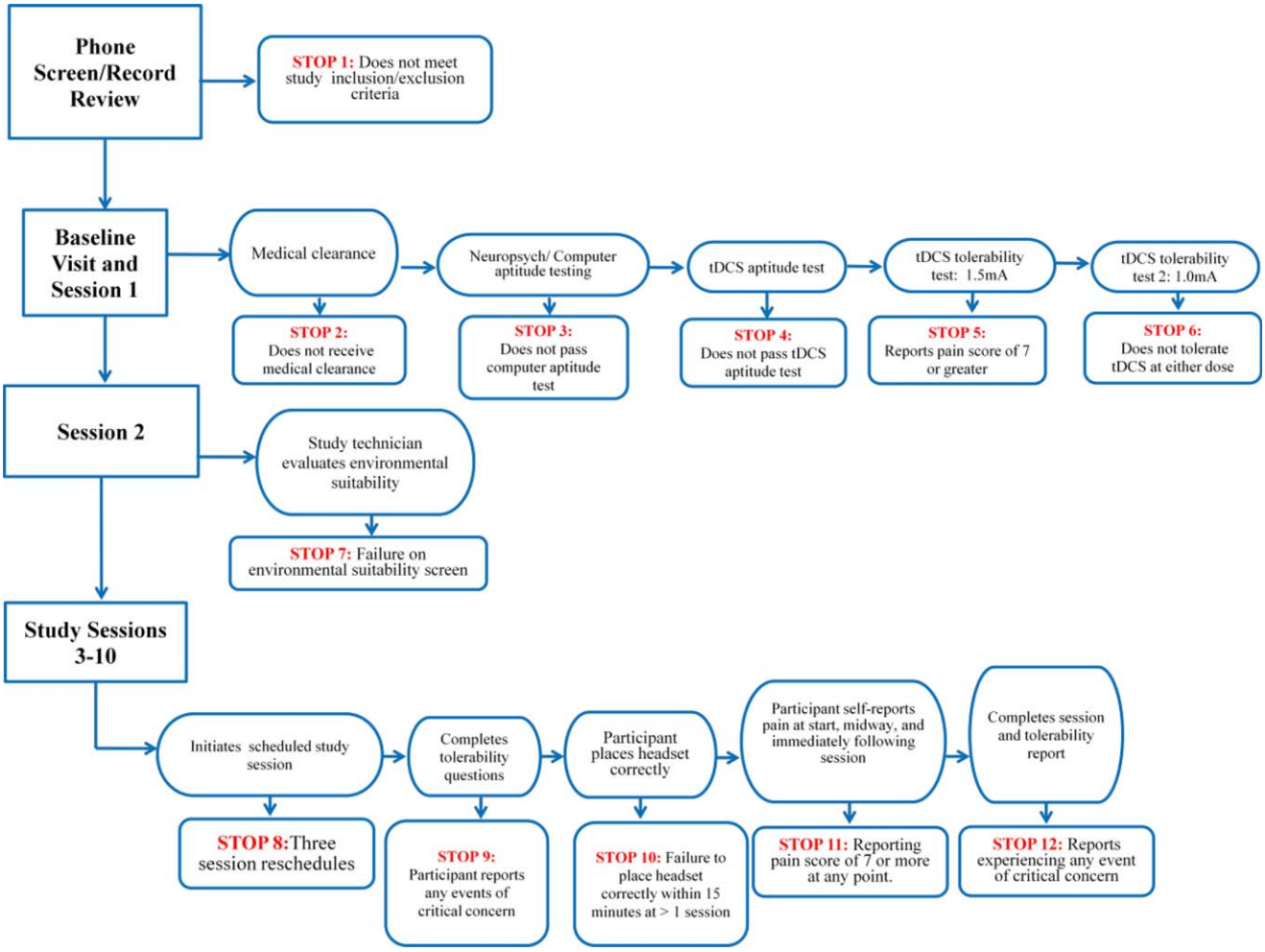

Figure 2. Stop criteria flowchart.

participant interaction. Study technicians recorded all participant measures on a daily basis and confirmed appropriate set-up, any events that occurred since the prior day's session, as well as a pain reading prior to providing the unlock code for the device.

Side effects were coded according to category and intensity, based on prior research trials (5,54). Any side effect rated moderate or higher was reported to the study PI. In addition, study technicians were made aware of the designated "stop criteria" that would indicate study termination for participants and referenced this chart throughout the study (Fig. 2). For the duration of each daily 20-minute tDCS session, the study technician remained connected to the participant. Participants were also required to have a portable or cellular phone accessible throughout the duration of the session to re-establish contact in the event that an internet connection might be lost.

Study End Visit and Equipment Return

After the 10th remote session, participants were scheduled to return to the clinic. Equipment was returned and the baseline evaluation measures were repeated.

Given the goal of the study was to develop trial methods, participants were compensated $100 dollars for baseline and study end visits, and $50 dollars for meeting pre-defined criteria for the successful participation in study procedures at each session (e.g., being ready and available for study procedures within 20 minutes of the scheduled time).

Study Outcomes

The primary outcome of this study was feasibility. As the study utilized a remote teleneurology protocol, we sought to match compliance, safety, and tolerability rates seen from protocols

Table 2. Study Measures.

	Baseline measures	Daily measures	Follow-up measures
Pain	PROMIS Pain (46,47)	Visual Analog Scale-Pain (50,51)	PROMIS Pain (46,47)
Fatigue	PROMIS Fatigue (48)	Visual Analog Scale-Fatigue (52)	PROMIS Fatigue (48)
Affect	PANAS (53)	PANAS (53)	PANAS (53)
Cognitive Processing Speed	ANT-I (44,45)		ANT-I (44,45)

Table 3. Sample Demographic and Clinical Features.

Gender	Female (%)	85%
	Male (%)	15%
Age	Mean (SD)	51 ± 9.25
	Range	30–69
EDSS (36)	Median	4.0
	Range	1.0–8.0
Years of education	Mean (SD)	16 (±) 2.55
	Range	12–20
Subtype	RRMS	6
	PPMS	2
	SPMS	12

administering tDCS in the clinic. Based on prior tDCS trials, we defined study success 80% participants completing at least 80% of the target number of treatments (i.e., 8 of 10 sessions). This rate is consistent with studies that have found that missed tDCS effects can be observed when one of five sessions per week is missed (55).

Secondary outcomes were changes in the symptom assessment administered at baseline and study end (Table 2). In the absence of a control (sham) comparison, these measures only provide a general indication of symptom response to inform the design of future controlled trials. Patients were not enrolled on the basis of any specific symptom experience, nor were they told to any specific symptom was targeted with the treatment in this methods study.

RESULTS

The study was met with strong demand by potential participants and rate of enrollment was controlled by device availability. Over the course of approximately six months, $n = 20$ MS participants were enrolled, with a waitlist of more than 30 interested candidates. Table 3 shows the participant characteristics.

Study Completion Rates

Nineteen of 20 participants (95%) completed at least eight sessions, meeting our compliance criteria set as completing four sessions per week for two weeks. All participants except three ($n = 17$) completed full ten study sessions. Of these three participants who failed to complete all sessions, one participant dropped out of the study after four sessions (attributed to a personal event concerning family and not related to tDCS or the study), and the additional two participants missed one session each due to a failure to attend the regularly scheduled session within the twenty minute window as defined by the study stop criteria.

Protocol Adherence

No session was discontinued for any participant, indicating 100% complete adherence during the stimulation protocol. Measures were easily collected remotely before and after the session, as well as with ratings during the midway of the stimulation period.

Tolerability

tDCS was uniformly well-tolerated. No adverse events were reported and no session was discontinued. Further, no participant reported any side effect of severe intensity for any session. Tolerability was consistent with what has been reported with clinic delivery of tDCS. As seen in Figure 3, and as expected, the most common report was for skin tingling, and this did not exceed a moderate intensity. Prior to each daily session, participants also completed a "before stimulation questionnaire" to confirm if any side effect continued following the prior day's session. None of the recorded side effects were reported to have lasted beyond 24 hours.

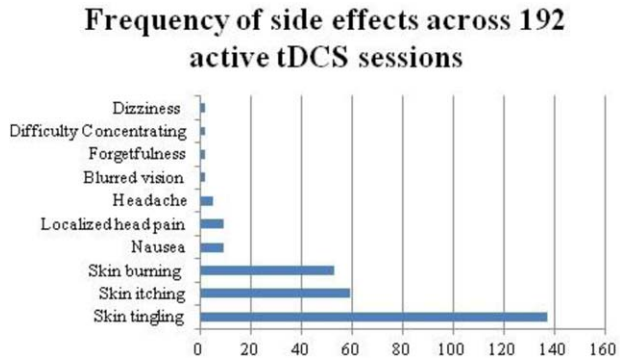

Figure 3. Side effects reported across active tDCS sessions using protocol ($n = 192$).

Secondary Outcomes

Confirming the positive response from previous controlled trials of tDCS in MS to date (13,15,21,23–25,30), we also observed improvement in all symptoms measured. These findings are descriptive only, as there is no control comparison and the participants were not uniformly experiencing any or all of the symptoms measured. There were also individual differences in response. Nonetheless, as a group, there was a consistent improvement from baseline across all symptoms measured: 27% decrease in cognitive processing speed (Attention Network Test-Interaction (44,45), Executive Network score), 10% increase in positive affect [Positive and Negative Affect Schedule or PANAS (53)], 24% decrease in negative affect (PANAS), 12% decrease in fatigue [PROMIS Fatigue (48)] and 14% decrease in pain [PROMIS Pain (46,47)]. While both promising and consistent with previous findings (13,15,21,23–25,30), these results are only preliminary and must be interpreted in the context of a control group before formally reporting in detail. Notably, the majority of participants, including the individual with early discontinuation, requested the opportunity to continue treatments beyond study end.

DISCUSSION

In this pilot study, we found that remotely supervised home delivery is feasible and well-tolerated for study in a diverse sample of MS participants using our structured protocol. The extensive procedures for remote supervision, including real-time monitoring through videoconferencing, ensure for safety and tolerability while also providing reliable and reproducible stimulation sessions.

Offering trial participation and treatment to those living with MS who otherwise would not be able to travel to the clinic to receive daily sessions allows us to include a wide range of the MS community for future study. For example, large surveys have indicated that the majority of the MS population face mobility challenges on a daily basis (56). The remote (at-home) access to tDCS was met with overwhelming positive feedback from the participants, particularly those with more advanced forms of the disease (e.g., 70% of our sample had a progressive form of MS) and general mobility issues that preclude them from participating in other study protocols. Additionally, our protocol allows for a greater number of sessions of tDCS to be studied in MS in order to determine optimal clinic

benefit. For example, to our knowledge only one prior study in MS has included more than five sessions in their design [also including 10 sessions, for cognitive benefit (30)]. Evidence suggests that multiple sessions of tDCS may be optimal for cumulative benefit and also when paired with rehabilitative programs such as at-home cognitive or physical exercises.

Other than device availability, our protocol's requirement for home visits was a rate limiting factor. We included these visits from an abundance of caution. However, home visits are not practical in many locations and may also provide too costly in terms of staff time and allocation. Equipment is rapidly evolving to lighter-weight tDCS units (e.g., powered by rechargeable lithium ion batteries), streamlined headset design with standardized placement, and the ability to teleconference through small handheld cell phones or tablets. With these considerations, our experience is that the home visits would not be necessary, and our next step will be to move from the baseline in-clinic training directly to remote use. Otherwise, this telemedicine approach to tDCS provides an economical option for future treatment.

We were met with strong patient interest to try tDCS treatments for a range of symptoms. The majority of participants reported some degree of clinical benefit (requesting to continue treatment) with group improvement observed across all symptoms measured. Future studies will include a sham condition to our protocol, which can be programmed into the devices in a double-blind design. The inclusion of sham will inform the direction for a controlled clinical trial using remotely supervised tDCS.

CONCLUSION

In sum, our remotely supervised protocol provides an option for delivering tDCS to those living with MS. With controlled study to determine parameters for optimal use, it has the potential to transform the standard of care for a range of symptoms in MS. If established as a clinical treatment, tDCS could be delivered through the telemedicine platform developed here.

Authorship Statement

Dr. Charvet, Ms. Kasschau and Ms. Sherman designed the study with intellectual input from Drs. Bikson and Abishek. Ms. Kasschau, Ms. Sherman and Mr. Reisner conducted the study including patient recruitment and data collection. Dr. Charvet and Ms. Kasschau completed the data analyses and drafted the manuscript. All authors approved the final manuscript.

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