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Remotely Supervised Transcranial Direct Current Stimulation Increases the Benefit of At-Home Cognitive Training in Multiple Sclerosis

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Objective: To explore the efficacy of remotely-supervised transcranial direct current stimulation (RS-tDCS) paired with cognitive training (CT) exercise in participants with multiple sclerosis (MS).

Methods: In a feasibility study of RS-tDCS in MS, participants completed ten sessions of tDCS paired with CT (1.5 mA × 20 min, dorsolateral prefrontal cortex montage). RS-tDCS participants were compared to a control group of adults with MS who underwent ten 20-min CT sessions through the same remotely supervised procedures. Cognitive outcomes were tested by composite scores measuring change in performance on standard tests (Brief International Cognitive Assessment in MS or BICAMS), basic attention (ANT-I Orienting and Attention Networks, Cogstate Detection), complex attention (ANT-I Executive Network, Cogstate Identification and One-Back), and intra-individual response variability (ANT-I and Cogstate identification; sensitive markers of disease status).

Results: After ten sessions, the tDCS group ($n = 25$) compared to the CT only group ($n = 20$) had significantly greater improvement in complex attention ($p = 0.01$) and response variability ($p = 0.01$) composites. The groups did not differ in measures of basic attention ($p = 0.95$) or standard cognitive measures ($p = 0.99$).

Conclusions: These initial findings indicate benefit for RS-tDCS paired with CT in MS. Exploratory analyses indicate that the earliest tDCS cognitive benefit is seen in complex attention and response variability. Telerehabilitation using RS-tDCS combined with CT may lead to improved outcomes in MS.

Keywords: Cognitive, multiple sclerosis, remotely supervised, tDCS, telerehabilitation

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. The remaining authors have no potential conflicts of interest to declare.

INTRODUCTION

Transcranial direct current stimulation (tDCS) is a relatively recent therapeutic development that utilizes low amplitude direct current ($\leq$2.0 mA) to induce changes in cortical excitability (1–4). tDCS is known to be safe and well-tolerated (5–8) with many advantages compared to other stimulation methods including ease of use, lower cost, and portability (9). It is theorized that pairing tDCS with rehabilitation strategies may lead to more meaningful and lasting benefit (10–14). A particularly promising application of tDCS is to improve the rate of learning (15–17) and magnitude of benefit from cognitive training (CT) (14,18–26). While many questions remain, pairing tDCS with CT has been shown to increase learning and cognitive performance, particularly in tasks of information processing and working memory (14,18,22,26–29).

Multiple sclerosis (MS) is the most common progressive neurologic disorder in adults of working-age (30) and is characterized by demyelination, immune-mediated inflammation, and central nervous system neurodegeneration. The most common subtype is relapsing-remitting and over half of these individuals transition to a

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progressive course; the remainder have a progressive course from the onset (31). tDCS warrants evaluation for potential clinical applications in MS (9,21,32–39). MS is associated with a high (>70%) rate of cognitive impairment. Those with MS also suffer from other symptoms including mood, fatigue, sensory and motor problems that may respond to tDCS as well (40–46).

A major obstacle for tDCS studies has been the requirement to travel to the clinic for repeated treatment sessions that may continue for weeks or even months. This travel requirement can be especially prohibitive for those living with cognitive and motor impairment, who may already be taxed with daily home and work responsibilities or, due to disability, be dependent on caregivers or others for basic transportation needs (41,43,45). To address this challenge, tDCS protocols offering home use are needed to improve access and enable larger trial designs.

We developed a remotely supervised at-home use protocol to deliver CT and tDCS to those living with MS (47–50). Using extensive criteria for safety and tolerability along with specially designed equipment, MS participants were successfully able to complete CT paired with tDCS from home (8,47). A clinical trial design that provides the option for patients to participate from home enables rapid recruitment. Moreover, a home-use protocol pairing tDCS with a therapeutic regimen offers scalability to pair tDCS with a range of rehabilitation approaches.

Here, we report the cognitive findings from our feasibility trial. To verify the protocol, tDCS participants completed the study along with a control group who completed the CT portion only using the remotely supervised methods. Participants completed a battery of standard and computer-based cognitive tests at baseline and study end, with change in performance compared between the conditions.

MATERIALS AND METHODS

This study conformed to the guidelines set by the Declaration of Helsinki and all study procedures were approved by Stony Brook University Institutional Review Board and the Committee on Research Involving Human Subjects. Participants were recruited between March of 2015 and February of 2016. Written, informed consent was obtained for all participants.

This study was an open-label and exploratory pilot study. Controls were separately recruited following the feasibility study for comparison. Eligibility criteria were the same for both conditions and relatively broad to match the primary aim of assessing the feasibility of the remote protocol. We enrolled 46 patients with a confirmed diagnosis of MS (all subtypes) between the ages of 18–70 years. One participant was unable to finish their sessions due to personal matters and was excluded from our analysis.

Participants were required to have had no MS relapses within the last 30 days (for disease stability), be English speaking, and the visual, motor, and cognitive capacity to understand consent and operate study equipment. All participants with an Expanded Disability Status Scale (EDSS) (51) of 6.5 or above (indicating more severe MS-related neurologic impairment) used a proxy or caregiver to assist with tDCS headset placement and device operation.

Study Procedures

We have carefully designed our remotely supervised protocols to maintain the standards of clinic-based treatment which enhanced our recruitment rate and treatment compliance for both CT (52) and tDCS (50).

Participants in both conditions completed the first session during their baseline visit to clinic. This first session established tolerability and capacity for self-administration for the tDCS group, and the control participants completed their first CT session. This session was then followed by nine remotely supervised sessions with real-time supervision though videoconferencing. Following current convention, sessions were completed once a day for five days per week. Active tDCS participants received 1.5 mA stimulation for 20 min while completing the computerized CT program.

Study equipment included laptops configured with a videoconferencing program (VSee (53)) and a program to allow for remote control of the computer by the study technician (TeamViewer (54)). For the daily sessions, the participant was only required to connect the laptop to the Internet, otherwise the study technician guided them through all procedures. Once the study technician had established connection with the participant and confirmed proper headset placement, a one-time use dose code was provided that unlocked the tDCS device for one 20 min session. The participant would then begin their daily session under real-time supervision.

Rigid stop criteria were included in the study protocol to ensure safety of participants. Pain associated with the tDCS device was monitored before, during, and after each session using a 1–10 visual analogue scale for pain (these procedures did not apply to control participants who did not undergo tDCS treatment). Any participant who reported pain of a 7 or higher resulted in abortion of the study session and discontinuation of subject's participation from the study. Common side effects of tDCS were also monitored before and after each session, ensuring that any significant or harmful side effects were recorded; these side effects, if severe, resulted in abortion of the study session and discontinuation from the study.

CT Program

To meet this study's objectives, we used a research version of Lumos Lab's (55) training platform specifically limited to tasks of information processing, attention and working memory systems. Limiting training to these exercises provided the opportunity to test proof of concept for the combined therapies within this shorter two-week time frame, and maximize the synergistic effect by engaging the same regions as targeted by the tDCS (see Fig. 1). Also, CT targeted to specific domains of impairment vs. broad spectrum may have greater utility in MS to ultimately tailor to a patient's specific needs (56).

The training consisted of five traditional tasks that have been demonstrated to lead to benefit, both with and without adjunctive tDCS (n-back, auditory and visual span, simple arithmetic, and match-to-sample (15,18,20,22,29,57–61)). Based on our experience, we have found these training tasks to be the best-designed with the highest compliance rates (e.g., reaching 80% or more of target playing time in a sample of ten pilot participants (52)).

The active condition consisted of ten 20-min sessions of (1.5 mA) tDCS paired with a CT program. The CT only condition consisted of ten 20-min sessions of training, following the same remotely supervised procedure without tDCS. Participants were administered cognitive assessments in clinic at their baseline study visit and at the post-intervention follow-up visit. Regardless of active or control condition, each session of CT was completed in 20 min.

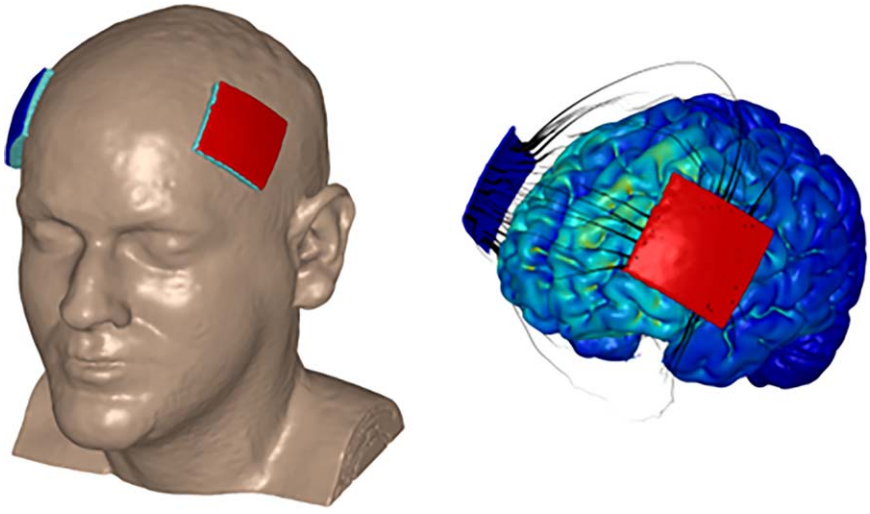

Figure 1. Working memory CT is associated with increased perfusion of left precentral gyrus/frontal middle gyrus/superior frontal gyrus. The "OLE" DLPFC tDCS montage is optimized to target similar regions (62). [Color figure can be viewed at wileyonlinelibrary.com]

RS-tDCS Study Equipment and Montage

Following completion of baseline assessments, active condition participants were trained on the methodology of the remote protocol. Active participants received a tDCS study kit containing a Soterix Mini-CT tDCS Device, a Soterix tDCS headset, electrode sponges for all ten sessions (5 × 7 cm), an informational packet, and saline solution. The Soterix tDCS headset was specially designed to provide easy and accurate electrode placement for home use. The study technician instructed participants on how to operate both the device and the laptop in detail. A short instructional video was also played to reinforce the instructions.

While frontally mediated processes have been broadly associated with complex attention, recent fMRI studies have demonstrated that working memory CT (e.g., n-back) is specifically associated with increased perfusion in the left precentral gyrus/frontal middle gyrus/superior frontal gyrus (Fig. 1) (58). Using specially designed equipment and an extensively optimized montage using the "OLE"-system targeted montage optimized for the dorsolateral prefrontal cortex (DLPFC) from Seibt et al. 2015, with the location of electrodes is close to an F3/F4 positioning with the anode placed on the left (F3) and cathode on the right (F4). This montage intends to increase benefit in areas of attention and working memory through stimulation of this target (62).

Cognitive Measures

Standard and computer-based tests of cognitive functioning, separate from the CT program, were administered at baseline and repeated at study end using alternate forms to minimize practice effects for the standard neuropsychological measures. In addition to the following study outcome measures, participants were administered the Wide Range Achievement Test 3 (WRAT-3) (63) which gives an estimate of premorbid cognitive ability.

Standard Cognitive Tests

Participants were administered the Brief International Cognitive Assessment in MS (BICAMS) (64). BICAMS is a brief, repeatable assessment of MS-related cognitive impairment which includes three neuropsychological tests: Symbol Digit Modalities Test (SDMT) (65), Brief Visuospatial Memory Test-Revised (BVMT-R) (66), and the Rey Auditory Verbal Learning Test (RAVLT) (67).

Measures of Basic Attention and Complex Attention

Participants were administered two computer-based tests of attention and information processing speed: the Attention Network Tests-Interaction (ANT-I) (68) and Cogstate Brief Battery (69). The ANT-I consists of 6 blocks with 48 trials each for a total of 288 trials. The participant is required to indicate the directionality (left or right) of the middle arrow in the series, but additionally the flanking arrows can be congruent (same direction as the middle arrow) or incongruent (different direction than the middle arrow). Auditory distractors (alerting tone of 2000 Hz for 50% of trials) are also included to provide an additional layer of complexity. Trial-by-trial reaction time is used to compute Orienting, Attention, and Executive Function network scores based on reaction time. Orienting and Attention Networks are based on simpler reaction time processes while Executive Network has been shown to be sensitive to information processing deficits in MS (70,71).

Cogstate is a validated, widely used cognitive testing platform with simple administration and repeatable forms (72). We used three Cogstate tasks: Detection (simple reaction time), Identification (choice reaction time) and One Back (working memory). Performance on each task is measured by response speed which reflects the subject's information processing time.

For both the ANT-I and the Cogstate Identification task we calculated intra-individual variability (IIV). IIV has been shown to be one of the earliest indicators of MS-related cognitive involvement (70,73) and gives a measure of consistency; higher IIV values correspond to less consistent reaction times and vice versa. IIV was calculated using a regression-based model from previous studies in MS (73). IIV values present the opportunity to analyze a dimension of consistency and variability not captured by the raw scores output from the aforementioned measures.

Across these measures, we calculated four composite performance scores:

1. A BICAMS composite consisting of the SDMT, RAVLT, and BVMT-R scores;
2. A basic attention composite (ANT-I Alerting and Orienting Network scores; Cogstate Detection);
3. A complex attention measure composite (ANT-I Executive Network; Cogstate Identification and One Back);
4. An IIV composite (across the ANT-I and Cogstate Identification task).

Table 1. Demographic and Clinical Characteristics.

Characteristic	Full sample ($n = 45$)	Active ($n = 25$)	CT Only ($n = 20$)	p value
Gender (% female)	75.56%	84.00%	65.00%	0.28*
Age (mean years ± SD)	51.96 ± 11.00	52.69 ± 9.49	51.00 ± 12.71	0.66
Education (mean years ± SD)	15.59 ± 2.43	16.15 ± 2.55	14.85 ± 2.01	0.11
Handedness (% right handed)	93%	92%	95%	0.69*
Disease Duration (mean years ± SD)	16.73 ± 9.15	17.71 ± 8.77	15.70 ± 9.64	0.49
MS Subtype (% RRMS)	44%	28%	75%	0.002*
Baseline WRAT-3 (mean years ± SD)	108.10 ± 8.96	109.16 ± 10.47	106.70 ± 6.61	0.41
		=	=	=

p values determined by independent sample t-tests completed comparing the tDCS + CT group and the CT only group.
*Indicates p-value determined by χ^2 test.

The directionality of these composites were adjusted so that scores above and below zero consistently indicated improvement and decline, respectively.

Analyses

For each composite measure, change from baseline was calculated across individuals. Next, the absolute change was transformed to a z-score for each measure (using the group's baseline performances for mean and standard deviations) to have each measure weighted equally. The change z-score for each of the measures was then averaged for one representative change score.

To determine benefit, the mean change z scores for each of the four areas (BICAMS, basic attention, complex attention, and IIV) were compared between the active and CT only conditions. Two-tailed, independent sample student's t-tests were used. SPSS version 23 was used for all analyses.

RESULTS

Participants

There was a total of 45 participants, 25 in the active group and 20 in the CT only group. Table 1 gives an overview of the demographic and clinical characteristics of our sample.

In both conditions, we found a high degree of compliance with >96% session completed. Feasibility data for our RS-tDCS protocol have been previously reported (47).

The baseline BICAMS composite was shown to be the same between the Active and CT Only group, indicating similar baseline cognitive impairment (Active mean baseline z-score = −1.09 ± 1.51 vs. CT Only = −0.86 ± 1.02, $p = 0.55$).

WRAT-3 baseline scores were also shown to be similar between the Active and CT only groups, indicating similar premorbid cognitive ability between both groups (Active mean = 102.92 ± 10.31, CT Only mean = 106.70 ± 6.61, $p = 0.41$).

Table 2. Baseline Cognitive Composite z-Score (Mean ± Standard Deviation).

Composite	Active		CT only		p value
BICAMS	−1.09 ± 1.52	$n = 24$	−0.86 ± 1.02	$n = 20$	0.56
Basic Attention	−0.03 ± 0.92	$n = 24$	0.03 ± 0.55	$n = 20$	0.78
Complex Attention	−0.02 ± 0.69	$n = 17$	0.31 ± 0.45	$n = 20$	0.09
IIV	−0.22 ± 1.22	$n = 17$	0.31 ± 0.38	$n = 20$	0.10

There were no significant differences between the active and CT Only group in baseline cognitive composite scores, shown in Table 2.

Efficacy for Cognitive Function

The Active and CT Only groups did not differ in change on the BICAMS score, with the same slight improvement noted in both groups (0.09 ± 0.47 vs. 0.09 ± 0.47, $p = 0.99$). Similarly, the groups also did not differ in change in basic attention (−0.01 ± 0.72 vs. 0.01 ± 0.32, $p = 0.95$).

However, on the two more sensitive measures, the Active group had significantly greater gains: complex attention (0.28 ± 0.53 vs. −0.25 ± 0.55, $p = 0.01$) and IIV (0.40 ± 0.84 vs. −0.33 ± 0.76, $p = 0.01$), as shown in Figure 2.

On average, measures of complex attention and IIV in the CT Only group indicated modest improvement in the Active group and decline in the CT Only group. Neither group's change reached one standard deviation or more, and would not be considered clinically meaningful. Instead, the absolute difference between the two groups provides an indication of the specific effects of tDCS.

DISCUSSION

Across ten training sessions, we found specific cognitive benefits of tDCS on sensitive measures of complex attention and IIV. This finding of cognitive benefit is consistent with what has previously

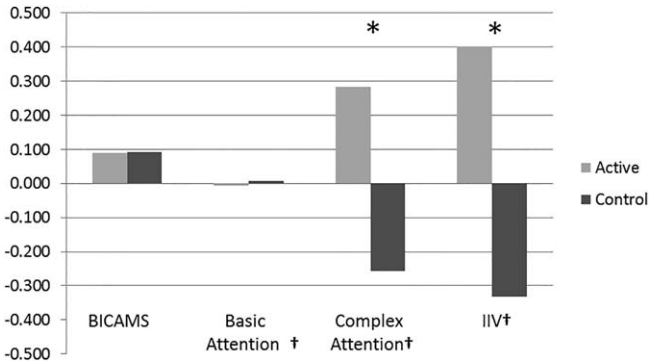

Figure 2. Change z-scores from baseline to follow-up are graphed. The directionality of scores have been adjusted so that positive change values indicate improvement and negative values indicate worsening (indicated by a †). Sample sizes and characteristics are listed in Table 3. (*) represent significant difference ($p \leq 0.05$) as determined by two-tailed independent samples t-test.

Table 3. Cognitive Composite Change Score (Mean ± Standard Deviation).

Composite	Active		CT Only		*p* value
BICAMS	0.09 ± 0.47	$n = 24$	0.09 ± 0.47	$n = 20$	0.99
Basic Attention	−0.01 ± 0.72	$n = 24$	0.01 ± 0.32	$n = 20$	0.95
*Complex Attention	0.28 ± 0.53	$n = 17$	−0.25 ± 0.55	$n = 20$	0.01
*IIV	0.40 ± 0.84	$n = 17$	−0.33 ± 0.76	$n = 20$	0.01

*Sample size is smaller for the Active group's performance in complex attention and IIV because some patients were unable to complete the required tasks due to the late addition of the task into the study and, in some cases, motor disability. However, these exclusions do not significantly alter the subtype proportion (% RRMS is 29% for the $n = 17$).

been reported with tDCS in a range of conditions presenting with cognitive impairment (17,23) and is also consistent with our study hypothesis regarding stimulation of the DLPFC (1). Further, we found that tDCS paired with CT, while utilizing our RS-tDCS protocol, is successful in reaching participants away from clinic and introduces the potential to include tDCS in telerehabilitation protocols.

While significant, the observed cognitive benefit is small. The groups differed on absolute change with the Active condition averaging toward improvement and the CT Only condition averaging toward worsening. A trend toward worsening in the CT Only group was not expected, and may instead represent general variation across testing. Neither group's change would be considered clinically significant (less than one standard deviation). However, the observed benefit of tDCS is found on measures that are often the most sensitive to detecting MS-related cognitive impairment (73–76). Trials in depression have shown that tDCS tends to show a dose-dependent trend (77). By increasing the number of sessions or increased amperage, greater benefit may be found from tDCS treatment.

Based on theorized increase in neuronal firing and synaptic activity, tDCS delivered simultaneously with CT is thought to selectively activate and reinforce the regions engaged in the cognitive activity (10,24,78) with the transfer of effects to similar tasks (15,20,25,79). Intensive repetitive targeted exercise may improve cognitive ability at the processing level, potentially through mechanisms of neural plasticity (re-organization of neural connections) (80–85). Cognitive enhancement with tDCS has been demonstrated with attention and working memory measures (18), a common area of deficit for MS (40,75,86–89). A recent trial has reported tDCS (DLPFC montage) paired with CT to improve cognitive functioning in patients with MS (23). Mattioli et al's study focuses on attention and information processing with $n = 20$ MS participants completing ten in-clinic tDCS sessions for a sham-controlled efficacy study. Using our at-home protocol and no sham control we still see evidence that tDCS augments CT, suggesting a reliable effect. Moreover, our study shows that these benefits are observed with a remotely supervised protocol, allowing broad patient inclusion and ease of access.

tDCS has been previously shown to modulate reaction time (90,91) when administered simultaneously with a working memory task. It is possible that this effect occurs in our study outcome measures, however we evaluated a cumulative benefit following numerous treatment session rather than direct change over the course of active stimulation. While several of our measures are reliant on reaction time (measures in the simple attention composite), others like our IIV measures are more complex and would be harder to skew from a monotonic effect. Future studies could include both change over the course of active stimulation along with the change following repeated stimulation sessions to better understand the influence of tDCS on reaction time.

In consideration of clinical disease features, there were a higher number of participants with a progressive subtype of MS in the tDCS condition. However, the samples were generally well-matched according to demographic and clinical descriptors. While there is a wide range of cognitive involvement across participants, and in MS in general, differences in cognitive functioning or response to treatment would not necessarily be expected to occur between the subtypes. Instead, progressive subtypes are considered to have more advanced disease but the nature of their cognitive impairment is the same and typically all subtypes are included together in studies of cognition and cognitive remediation. However, future studies should more closely account for any role of disease status in the interpretation of results.

A limitation of our study is the use of open-label tDCS and absence of a sham-controlled condition. However, the CT was identical for both conditions and all participants completed the same procedures to train through videoconference supervision and real-time monitoring. The sham is important for neutralizing the influence of a placebo effect. However, it could be argued that both participant groups had similar expectations of cognitive benefit given that they were both completing CT tasks. Also, the selective benefit on our most sensitive measures, and especially in the measure of IIV, suggest against a primary placebo effect. Another limitation is our broad inclusion criteria, as our study was focused on the feasibility of the remote method. In future trials, careful selection of participants based on focused study criteria is important to increase power.

CONCLUSIONS

Our RS-tDCS protocol is an effective method to deliver tDCS and CT at home. In a varied sample of participants with both relapsing-remitting and progressive subtypes, greater improvement in cognitive processing and IIV as compared to CT only group were found. This effect, while modest, indicates the benefit of our RS-tDCS protocol paired with CT in MS.

Authorship Statements

Dr. Charvet, Ms. Kasschau, Mr. Shaw, and Ms. Sherman designed the study with intellectual input from Drs. Abishek, Bikson and Krupp. Ms. Frontario, Ms. Kasschau, Mr. Shaw, and Ms. Sherman conducted the study including patient recruitment and data collection. Mr. Zeinapour contributed the modeling for the study. Dr. Charvet, Mr. Dobbs, Ms. Frontario, Ms. Kasschau, and Mr. Shaw completed the data analyses and drafted the manuscript. Drs. Charvet, Bikson, Datta, Mr. Dobbs, and Mr. Shaw reviewed and edited the manuscript. All authors approved the final manuscript.

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