

features such as irritability and anxiousness as part of general participation in the study.

Future studies will utilize neuroimaging to confirm targeted engagement of the DLPFC in order to enhance changes in mood with tDCS in MS participants. We will also characterize changes in mood in participants with clinically significant mood problems at baseline. We hope that tDCS treatment may be generalizable across conditions.

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## PROCEEDINGS #12. REMOTELY-SUPERVISED TRANSCRANIAL DIRECT CURRENT STIMULATION (RS-tDCS) FOR PARKINSON'S DISEASE (PD) CLINICAL TRIALS: GUIDELINES AND FEASIBILITY

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### 1. Abstract and Introduction

Cognitive and motor deficits are common debilitating symptoms for individuals living with Parkinson's disease (PD). The severity of cognitive and motor impairment in PD is associated with disease burden and quality of life. (1, 2) Transcranial direct current stimulation (tDCS) is a recent therapeutic development with the potential to ameliorate symptoms of PD. Previous studies have associated tDCS with improvement in motor and cognitive function in patients with PD. (3) However, multiple treatment sessions are necessary for a cumulative benefit. The requirement to travel for daily clinic treatment sessions presents an obstacle for many patients, especially those with higher disability and limited access to transportation. In addition to restricting patient access to repeated treatment sessions, such challenges have also limited the design of clinical trials in PD to date. Recently, we have developed a remotely supervised tDCS (RS-tDCS) protocol that delivers computerized cognitive training (CT) paired with tDCS to individuals with MS. (4) Using the same protocol with extensive safety measures, well-defined guidelines, and specially-designed equipment, we explored the feasibility and adaptability of our RS-tDCS approach for participants with PD.

### 2. Methods

This study was an open-label feasibility study. The eligibility criteria were relatively broad, with the key factors being a definite diagnosis of PD, PD-related changes to cognitive functioning, adequate home facilities, and a score of  $\geq -3$  standard deviations on the Symbol Digit Modalities Test (SDMT(5)) to measure disease-related cognitive decline and to ensure that participants had the cognitive ability to understand and participate in study procedures.

Each participant completed 10 tDCS sessions (20-minute each, 1.5-2.0-mA, dorso-lateral prefrontal cortex or DLPFC montage, which has been verified for effective targeted engagement of fatigue in patients with PD(6), over a span of two weeks using the remotely-supervised protocol. After the initial session at baseline, participants were sent home with a study laptop and tDCS equipment. The tDCS device (Soterix Mini-CT) is dependent on a code to operate, delivering a single 20 minute "dose" per code. All sessions were supervised in real-time using videoconferencing. The tDCS study technician ensured that the headset was correctly placed before providing the single-use activation code for the session. Additionally, study technicians followed a decision-tree series of checkpoints with "STOP" criteria set forth in the protocol that must be cleared in order to proceed at each step. These checkpoints address compliance (attendance and ability to complete the procedures as instructed) and tolerability (if any predefined events are reported at any time or if pain crosses a threshold, participation will be discontinued). For each study session, participants in both conditions were asked to complete a self-report inventory of adverse events and common side effects before and after their sessions (with items derived from a list of the most common tDCS side-effects in previous trials.(7) During the stimulation sessions, participations completed cognitive activating tasks on the computer. Feasibility of the approach was assessed based on the aforementioned series of checkpoints to address attendance, tolerability, and safety of the sessions.

### 3. Results

A total of 50 sessions were completed with 100% compliance. In comparison to the MS sample (n=20) in our RS-tDCS pilot study, the PD participants (n=5) are significantly older (mean = 45.15 in MS vs. mean = 69.80 in PD, p=0.004). The PD cohort exhibited a slightly lesser degree of cognitive impairment in their corresponding age groups as measured by the SDMT (mean z-score = -0.94 in MS vs mean z-score = -0.66 in PD, p=0.90). However, this may be influenced by the higher level of education (mean = 17.4 years) achieved by participants in the PD cohort compared to those in the MS cohort (mean = 15.95 years, p = 0.21), and in addition, inter-individual variability will prominently influence a sample's demographic and disease feature composition in a smaller sample size. All participants were able to quickly learn self-administration. In addition, our RS-tDCS protocol provided the opportunity to coordinate sessions with participants' anti-PD medications, ensuring that CT-paired stimulation could occur within the crucial 1-3 hour time window post-medication for maximum benefit (as recommended by study physicians at the New York University Fresco Institute for Parkinson's and Movement Disorders). No serious adverse events were reported. The most commonly reported side effects were skin tingling and burning sensations. The most intense side effect was a burning sensation at an intensity of 4, which qualifies as "mild" on scale from 1 [minimal] to 10 [severe]. The intensity and duration of time that these side effects were noticed by participants tended to decrease throughout the study. Across the 50 sessions, 96% of the daily self-reported pain ratings related to stimulation that were taken before, mid-way, and after tDCS stimulation were reported as 0, which denotes "no pain" on the visual analog scale ranging from 0-10 that participants used to rate pain from the headset. RS-tDCS range of 1.5-2.0mA was tolerable for all participants in the study.

### 4. Discussion and Conclusion

The RS-tDCS protocol was originally developed and tested in MS participants but designed to be appropriate for more generalizable use. Here, we expand the RS-tDCS protocol for use in PD. The study's high rate of compliance indicates that RS-tDCS is a safe and feasible approach for delivering direct current stimulation for individuals with PD, as with MS, despite the older age of our cohort of participants with PD. Across all 50 sessions, participants with PD found the stimulation to be tolerable. Key concerns for implementing RS-tDCS as an at-home treatment for PD include overall apprehension of technology and the need for technological support among this cohort, given the advanced age range and disabilities. Overall, the data indicate that RS-tDCS is easily implemented to accommodate participants' medication schedules, as well as physical therapy and exercise schedules, to provide maximum benefit and convenience. These findings support the use of the RS-tDCS protocol for clinical study in PD and other movement disorders, as well as the generalizability of the RS-tDCS approach for participant cohort with varying neurological diseases aside from MS.

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### PROCEEDINGS #13. UPDATED SAFETY AND TOLERABILITY OF REMOTELY-SUPERVISED TRANSCRANIAL DIRECT CURRENT STIMULATION (RS-TDCS)

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### Abstract

Transcranial direct current stimulation (tDCS) is a promising therapy with a growing number of applications. However, clinical studies to date have been limited by small sample sizes and few sessions studied. To increase enrollment and extend treatment, we developed a protocol for remotely-supervised or RS-tDCS to enable participants to receive treatment from home while monitored in real-time. 1, 2 Here we present the findings of two studies in multiple sclerosis (MS), the first being an open label feasibility study with 1.5mA x 20 minutes and the second being a randomized, controlled clinical trial of active 2.0mA or sham x 20 minutes. In addition, we have extended the protocol for use in Parkinson's disease (PD), completing 10 open-label 2.0 mA sessions x 20 minutes. All sessions were performed using a dorsolateral prefrontal cortex montage (DLPFC) and were paired with cognitive training tasks. This study adds to previous safety evidence. 3

### Methods

Eligibility criteria were purposefully broad in both studies to assess the feasibility of a remote-supervision protocol. The criteria required that patients had a definite diagnosis of MS (all subtypes), were between the ages of 18-70, had no history of serious brain trauma, and were physically, visually, and cognitively competent enough to perform study procedures. Additionally, participants were required to enroll in the study with a healthcare proxy if their disability was greater than an Expanded Disability Status Scale (EDSS) Score of 6.5. Eligibility criteria for the Parkinson's Disease (PD) cohort was similar to the MS criteria, albeit with a larger age range for participation (30-89) and without the EDSS score requirement. The RS-tDCS protocol included a baseline screening and tolerability test, followed by training in device operation. Participants were then sent home with a study kit that included a laptop computer and tDCS equipment. Each remote session was self-administered with guidance from a study technician, while constant supervision was maintained via videoconferencing. Extensive safety and stop criteria were followed to prevent any adverse events or misuse. The studies used the Soterix Mini-CT device that delivered a 20 minute session of a specific current "dose" or sham, based on a preprogrammed one-time use code that was provided by the study technician at each session. Safety and tolerability were measured by assessing both experiences of minor adverse events and pain ratings. Following each session, participants were asked if they had experienced any adverse events, which were read aloud from a list of those

most commonly reported. Pain ratings (using a visual analogue scale, 1-10) were measured before, during, and after each session. Any participants experiencing pain or adverse events above an intensity of seven were discontinued from the study as per study protocols.

### Study 1

MS participants (n=26) were recruited between the dates of March 2015 and February 2016 at the Lourie Center for Pediatric MS at Stony Brook University. This trial was an open-label study and all participants knowingly received the active tDCS therapy. 1.5mA of tDCS therapy was administered for 20 minutes each day for 10 days.

### Study 2

Participants with MS (n=15) were recruited between January 2016 and September 2016 at the MS Care Center at New York University Langone Medical Center. This study is an ongoing, actively recruiting, randomized, double-blinded, controlled clinical trial using RS-tDCS.

All MS patients were randomized to either the active condition (20 minutes of 2.0mA tDCS) or the sham condition. The sham condition served as the control in this study and aimed to deceive participants into believing they were receiving the 20 minutes of tDCS by ramping up at the first minute of the session and ramping down at the last minute of the session. All participants who received the sham condition were offered 10 sessions of 2.0mA open-label tDCS following completion of 20 sessions of sham.

### Study 3

Participants with PD (n=4) were recruited between the dates of June 2016 and October 2016 at the Fresco Institute for Parkinson's and Movement Disorders at the New York University Langone Medical Center. Using the aforementioned remotely-supervised protocol established for MS, participants in the PD cohort received open-label 2.0 mA tDCS for 10 sessions to assess the feasibility and generalizability of the remotely-supervised protocol for this new cohort.

### Results

#### Study 1

Patients with MS (n=26) were recruited and completed study procedures. Two patients were discontinued during the course of the study. The first of the two was discontinued due to personal obligations, and the second was discontinued due to extreme sensations of skin burning (8.5/10 on the analogue scale) without any physical burns. The burning sensation did not continue after termination of the session. Overall, 248 sessions were successfully completed with this cohort.

#### Study 2

Patients with MS (n=17) were recruited and completed study procedures. Only one participant was discontinued from the blinded active condition due to serious headaches at an intensity above 7. One participant who was originally assigned to the sham condition and who opted for the extended, open label sessions voluntarily withdrew due to resurgence of headaches (the headaches did not meet our criteria of discontinuing the patient). 147 sessions of the active 2.0 blinded condition were successfully completed. 135 shammed sessions were successfully completed. 54 sessions of the open-label, extended sessions following sham were completed.

#### Study 3

Participants with PD (n=4) were recruited and completed study procedures. No participants voluntarily withdrew from this cohort nor were any discontinued. 40 sessions were successfully completed. In total, 624 sessions have been completed using the RS-tDCS protocol. Three participants have been discontinued and one has voluntarily withdrawn from the study. Participants who were discontinued due to adverse events found that they reverted to their baseline state when terminating the intervention. The percent of adverse events experienced is presented below in Fig. 1. This Figure does not include information regarding the intensity or duration of the adverse events experienced. Instead, it reports the frequency of adverse events experienced, which accounts for the high incidence rate of adverse events in the sham condition. Table 1 accounts for the intensity of the most commonly reported adverse events. The table also includes the number of adverse events reported relative to the number of total sessions. On average, an intensity above 3 was not reported for any of the most common adverse events in any stimulation condition.