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Tolerability and feasibility of at-home remotely supervised transcranial direct current stimulation (RS-tDCS): Single-center evidence from 6,779 sessions

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ABSTRACT

Introduction: The ability to deploy transcranial direct current stimulation (tDCS) at home is a key usability advantage to support scaling for pivotal clinical trials. We have established a home-based tDCS protocol for use in clinical trials termed remotely supervised (RS)-tDCS.
Objective: To report the tolerability and feasibility of tDCS sessions completed to date using RS-tDCS in clinical trials.
Methods: We analyzed tolerability (i.e., adverse events, AEs) reported in six Class I/II/III trials using RS-tDCS to study symptom outcomes over 10 to 60 daily applications. Across the six clinical trials, 308 participants (18–78 years old) completed an average of 23 sessions for a total of 6779 RS-tDCS administrations. The majority of participants were diagnosed with multiple sclerosis, and open-label trials included those diagnosed with a range of other conditions (e.g., Parkinson's disease, post-stroke aphasia, traumatic brain injury, cerebellar ataxia), with minimum-to-severe neurologic disability. Clinical trial feasibility (i.e., treatment fidelity and blinding integrity) was examined using two Class I randomized controlled trials (RCTs).
Results: No serious AEs occurred. Across administrations, three sessions (0.04%) were aborted due to discomfort, but no participant discontinued due to tolerability. The AEs most commonly reported by participants were tingling (68%), itching (41%) and warmth sensation (42%) at the electrode site, and these were equally reported in active and sham tDCS conditions. The two Class I RCTs resulted in rapid enrollment, high fidelity to treatment completion, and blinding integrity.
Conclusions: At-home RS-tDCS is tolerable, including when used over extended periods of time. Home-based RS-tDCS is feasible and can enable Class I tDCS clinical trial designs.

1. Introduction

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that passes a low intensity electric current through electrodes placed on the scalp [1]. tDCS is targeted to modulate brain regions of interest for behavioral or clinical effect [2]. Clinical trials of tDCS are now numbered in the hundreds, spanning investigation of its use for the management of neurological and psychiatric conditions. Both human and mechanistic trials show a cumulative benefit across stimulation sessions [3–5], presenting a practical obstacle for many investigators when participants are required to travel to the clinic or lab facility for daily treatment. Deploying tDCS for home use in clinical trials, defined by the FDA as "users in any environment outside of a healthcare

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facility" [6], can reach more participants and accommodate an extended number of tDCS sessions that may be necessary for adequate evaluation of its effect. There is a growing body of trials using approaches to home-based delivery of tDCS ([7–16]), with interest and urgency increasing in response to the COVID-19 pandemic [17].

Our lab has developed and verified a protocol to provide participants with home-based tDCS for use in our clinical trials [18–21]. Utilizing live remote supervision at each administration via videoconference, the protocol aims to replicate the standards of onsite tDCS administration in the clinic or lab, and is referred to as remotely supervised or RS-tDCS [20]. Similar supervised home-use tDCS protocols are being implemented by investigators to study tDCS in a range of conditions (e.g. Ref. [7–16]).

We initially developed and verified the RS-tDCS protocol in pilot studies in individuals with MS (administering 244 RS-tDCS sessions) [18,19,22,23]. Due to the nature of the disease, participants with MS range in age across the lifespan and have a diverse disease course, characterized by variability and broad-spectrum symptoms that can include cognitive and/or motor impairments as well as symptoms including fatigue, pain and mood disturbances. Given our goal to complete clinical trials of tDCS in the management of multiple sclerosis (MS), our procedures have been optimized to reach participants who are demographically diverse with varying levels of neurological impairment and to allow for the simultaneous pairing with therapeutic cognitive or motor training.

Following its development, we have found that the RS-tDCS protocol can be generalized for use in participants with other neurological conditions. Our RS-tDCS protocol has been validated for use in Parkinson's disease (PD) [24,25], and used in participants with post-stroke aphasia, cerebellar ataxia, depression, neurocognitive disorders due to traumatic brain injury, and mild cognitive impairment [26–28]. RS-tDCS has been successfully implemented at additional centers (e.g., for post-traumatic headache [29]), and we also provide at-home tDCS treatment through our tDCS telehealth clinical program (n = 113 patients have received clinical treatment to date, with 4,660 at-home tDCS sessions delivered) [30].

We have completed six clinical trials at NYU Langone Health using the RS-tDCS protocol. We report the aggregated tolerability data across these trials, including for protocols administering tDCS for extended treatment periods, and the feasibility of its use for the completion of Class I RCTs.

2. Methods

We report here from our six Class I/II/III trials at NYU Langone Health using the standardized RS-tDCS protocol [20] (Table 1). All studies were approved by the NYU Langone Health IRB and participants signed an informed consent prior to their participation.

2.1. RS-tDCS eligibility criteria

RS-tDCS protocols required participants to be at least 18 years of age, to have an estimated premorbid cognitive ability in at least the average range, and to be without severe current cognitive impairment. These criteria were screened for with a measure of single-word reading recognition (WRAT-4). Accommodations for those in the open-label trial for chronic neurological conditions with impaired language and/or visual functions included the nonverbal alternative tests of receptive vocabulary (Peabody Picture Vocabulary Test, 4th edition; PPVT-4) or expressive vocabulary (Wechsler Abbreviated Scale of Intelligence, 2nd Edition; WASI-II). Current level of cognitive impairment was estimated with the Symbol Digit Modalities Test (SDMT; using cut off age-normative z-score of < -3.0 SD).

Exclusion criteria for the RS-tDCS protocol included: (1) metal implanted in the head or in the neck; (2) pregnant or breastfeeding; (3) history of head trauma (e.g., head injury, brain surgery); (4) history of or current seizure disorder; (5) presence of any skin disorder or skin sensitive area near stimulation locations; (6) comorbid primary medical, neurological or psychiatric condition that was judged to be contributing to the enrolling symptom targeted by the clinical trial.

Full participant eligibility criteria varied by trial depending on targeted outcome measures (see Table 1). Four of the six trials were

Table 1
Descriptive characteristics of the randomized double-blind controlled clinical trials and open-label trials using the RS-tDCS protocol.

Clinical Trial Identifier	Diagnosis, n Participants	Time period	Study Design	Number of Sessions	tDCS Current Intensity (mA)	Electrode Montage	tDCS Duration (min)	Paired Activity
Class I								
NCT03838770	MS, 107	Mar 2019–Jun 2021	Sham-controlled RCT	30	2.0	DLPFC	20	Cognitive Training
NCT03499314	MS, 64	April 2018–Oct 2021	Sham-controlled RCT	20	2.0	M1-SO	20	Manual Dexterity Training
Class II/III								
NCT02746705	MS, 74	April 2016 –Sept 2018	Sham-controlled RCT	20/40	2.0/2.5	DLPFC	20	Cognitive Training
NCT03564496	MS, 32	Jul 2018–Oct 2021	Open Label	20	2.0	DLPFC	20	Cognitive Training
NCT02746705	PD, 16	April 2016 –Sept 2018	Open Label	10	2.0	DLPFC	20	Cognitive Training
NCT03049969	Major Depression, 3; Post-stroke Aphasia, 3; Neurocognitive Disorder, 3; MS, 2; Chronic Fatigue Syndrome, 1; Idiopathic Hypersomnia, 1; Cerebellar Ataxia, 1; Chronic Pain, 1	Sept 2017–Ongoing	Open Label	Up to 60	2.0–2.5	DLPFC/cerebellar montage	20	Cognitive Training, Physical Exercise

studies of participants with MS; an open-label trial included participants with PD, and the remaining trial enrolled participants with a range of other conditions. All participants were required to have a medically confirmed diagnosis of their presenting condition per trial definition, with stable disease and no change in any medication for at least one month prior to enrollment.

2.2. RS-tDCS equipment

The participants were loaned a study kit for the duration of their trial participation that included three key components to enable the RS-tDCS protocol (Fig. 1):

tDCS Device: All trials used a 1 × 1 mini-CT tDCS device (Soterix Medical Inc.). The mini-CT tDCS device is equipped with multiple safety features to allow at-home use. The device contains contact quality monitoring and control systems that update performance and feedback >1000 times per second. During the stimulation period, the 1 × 1 mini-CT device shows in real time the contact quality of the electrode using simple category levels: *Poor* vs. *Moderate*/*Good*. The stimulation will not start until adequate contact quality is achieved (*Moderate*/*Good*). Once adequate contact quality is achieved, it is rare for the contact quality to drop. If the contact quality moves to "*Poor*" during the stimulation period, the participant and the study technician are alerted by the device beeping continuously. The device will pause automatically if the contact quality is not restored, accompanied by an alert sound. The protocol guides the technician to instruct the participant in corrective action (e.g., typically applying pressure to the electrode). This high sensitivity to any change supports safety and helps to maintain stimulation efficacy. If there is any disruption in the contact quality for more than 30 s, the device automatically and gradually powers off, decreasing the current over 30 s. The device also has an *Abort* function that gradually ramps down the current in the event of undue pain or any desire to stop the stimulation to support tolerability.

The device has a code-based unlocking function that uses unique one-time activation codes for each stimulation session. Codes are provided at the time of the RS-tDCS session to the participant for device use by the supervising technician, as per the protocol.

Blinding and Sham Procedures: In the double-blind, sham-controlled RCTs, tDCS procedures were the same for active and sham tDCS. To maintain double blinding integrity, devices were pre-programmed in advance by an independent staff member who did not interact with the participant for the daily session or outcome assessments. For active tDCS, the device was programmed to ramp up to the target current intensity (for 30-s), provide constant current throughout the session (19 min), and then ramp down at the end (for 30-s). For sham tDCS, the device was programmed according to convention to ramp up to target current intensity (for 30-s) followed by a ramp down (30-s), with no current delivery for 18 min, and then ramp up (for 30-s) and down (for 30-s) at the end.

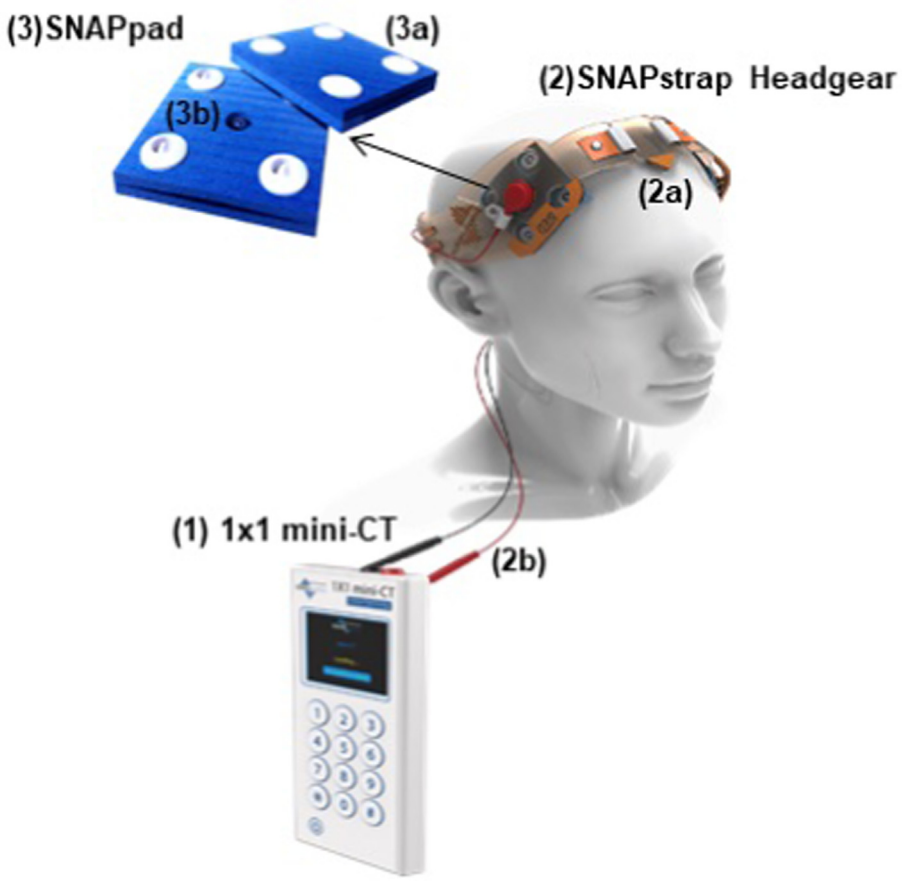

Fig. 1. RS-tDCS Equipment. (1) 1 × 1 mini-CT tDCS device: pre-programmable session type (active, sham), stimulation duration, and current intensity; generation of single-use "unlock-code" for pre-programmed dose. (2) SNAPstrap headgear: "cap"-like placement for simple positioning and uniform electrode placement; (2a) markers for guidance in placement; (2b) electrode polarity labeling with fixed wiring. (3) SNAPpad: (3a) individually-packaged pre-moistened sponge; perforated packaging for easy opening; (3b) snap connectors.

An exception was the sham programming for Trial NCT03838770 that included three periods of 60-s ramp up/down (beginning, midway, and end).

Headset and Electrodes: RS-tDCS used the Soterix Medical SNAPstrap headset that allows robust fixed position electrode placement for precise reproduction of a variety of montages. The headset included pre-saturated sponge electrodes (SNAPpads) in single use individual packaging for easy "snap" placement onto the headset for each session (Fig. 1). This specific headset ensures reliability of current flow and has been demonstrated to be consistent when tDCS is administered either onsite or from home [31,32]. As reported in Fig. 2, the electrode montages included in our trials were:

A. DLPFC montage, with the anode placed over the left dorsolateral prefrontal cortex (DLPFC) and the cathode over the right DLPFC (F3-F4, according to 10–20 EEG system);
B. M1-SO montage, with the anode placed over the left primary motor cortex and the cathode over the contralateral supraorbital area (C3-Fp2, according to 10–20 EEG system);
C. Cerebellar montage, with the anode placed over the cerebellum region (O2, according to 10–20 EEG system) and the cathode on the right shoulder.

Study Laptop: Pre-configured laptops were provided to the participant with a HIPAA-compliant video conferencing software (VSee), a remote monitoring software (TeamViewer), and the study session data reporting software. Depending on trial design and treatment outcomes, participants were also provided with additional software and/or equipment to complete the paired training activity (see Table 1).

2.3. RS-tDCS protocol

An initial visit (in person or remote) was provided for device orientation, training, and tDCS tolerability testing. All remaining tDCS sessions were then completed by the participant from home and monitored by study technicians in real time via videoconference. The supervising tDCS technicians were research lab personnel who completed our standardized training to administer the RS-tDCS protocol for daily sessions, ranging in background from doctoral level neurology faculty (PhD/MD) to advanced student interns.

Initial Baseline Training Visit: After the study screening visit, participants progressed through a series of checkpoints and training procedures following the standardized RS-tDCS protocol [18–20] (Fig. 2).

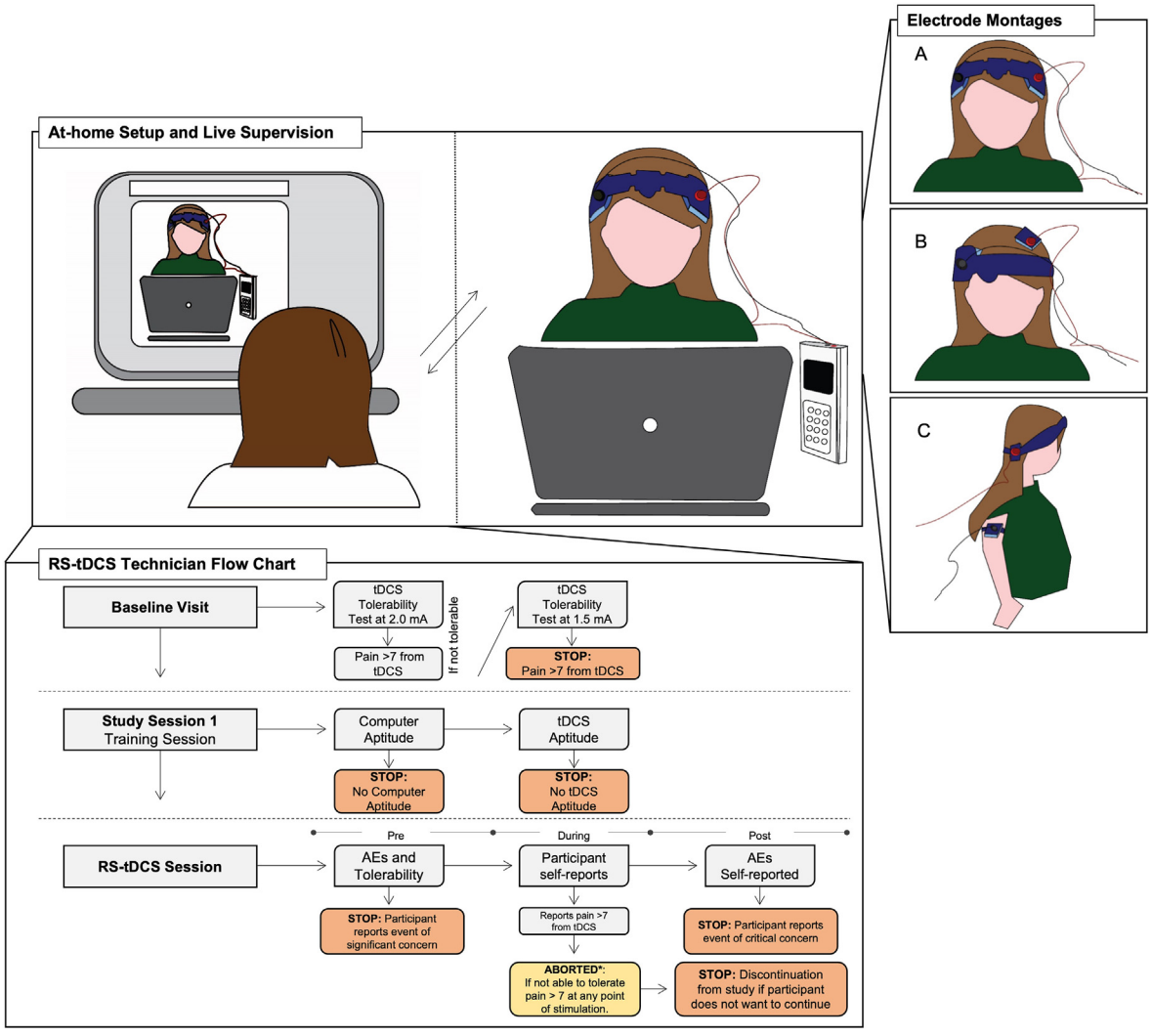

Fig. 2. Operationalization of daily RS-tDCS session. At-home setup, live supervision, electrode montages (A: DLPFC; B: M1-SO, C: Cerebellar), and RS-tDCS protocol.

Baseline Tolerability Test: During the initial visit, participants completed a 90-s tolerability and dose selection test. The 90-s tolerability test was performed with a standardized procedure by using the *Tolerability* function of the Soterix Medical mini-CT device. Testing begins at the electrical current intensity as defined by the study protocol (e.g., 2 mA or 2.5 mA). During the tolerability test, the current intensity is ramped up to the target intensity and then down over a 90-s period, with tolerability determined by participant ratings below 7 on the 0–10 Visual Analogue Scale (VAS) of pain. Participants unable to tolerate the target current intensity were given the option to proceed with another tolerability test at a lower amperage (reduced by 0.5 mA). In the event that this lower amperage was also intolerable, the participant was excluded from further participation in the study. The current intensity determined during the tolerability test was delivered during the duration of the intervention.

Daily RS-tDCS Sessions: Sessions were conducted daily Monday through Friday for 20 min with the electrical current intensity set between 1.5 and 2.5 mA as defined by the study protocol and individual participant tolerability levels determined at the baseline visit. The technician guided the headset placement and visually confirmed the correct position using the headset markers for guidance. When ready to begin, the participant was then provided with their single-use code to activate the daily session.

2.4. Session discontinuation criteria

During the session, the study technician captured any pain or discomfort spontaneously reported and with a specific query at the midpoint of the session. If the participant reported pain or discomfort at any point, they were asked to rate the intensity (VAS 0–10). In the event of pain related to stimulation that was rated higher than 7 on the VAS, the session was paused for review with the study technician. The protocol provides the option to abort the session, or resume the session based on participant feedback and repeated VAS administration. If the reported discomfort resolved and was addressed, the participant could choose to continue the session (see Fig. 1).

2.5. AE reporting

At the end of each stimulation session, participants were asked about any side effects that they experienced. In the absence of established AE reporting for the tDCS field, this process was initially completed with a rating of 11 potential AEs (adapted from Brunoni et al., 2011 [33]) for occurrence, intensity and duration. In addition, participants could also report other treatment-related experiences for AE reporting capture. Based on the predominant reporting of tingling/itching/warmth sensations across ratings and inconsistent endorsement of any other AE, we moved this process to a branched logic screen capture (vs. technician recording) delivered through an in-house software program developed specifically for use in RS-tDCS trials. Here, when a participant reported an AE, they were first asked about these three AEs, followed by a spontaneous capture of any “Other” AE experienced rather than continued prompting of each checklist item. In both the written checklist and the automated screen capture, participants were asked to report AE intensity on the VAS and the duration in minutes as guided by the tDCS technician.

2.6. Statistical analyses

We used descriptive statistics to summarize the clinical and demographic characteristics, trial enrollment, and completion rates. An AE occurrence was coded if reported at any intensity or duration. AE occurrences were examined by the percent of participants reporting an AE in at least one of their tDCS sessions, as well as by the percent of sessions in which an AE was reported. Then, we reported the percent of participants endorsing an AE in relation to stimulation condition (active, sham tDCS), current intensity (2.0, 2.5 mA), electrode montage (DLPFC, M1-SO) and population characteristics (e.g., clinical characteristics, sex, age). Chi-Square Fisher's Exact Test was used to assess whether the percent of participants endorsing each AE differed across the independent variables. We utilized Cochran's Q test to assess differences in the percent of participants reporting AEs of tingling, itching and warmth sensation at different time points (20 M1-SO sessions, 30 DLPFC sessions). Analyses were performed using SPSS 25.0. Level of statistical significance was set at 0.05 for all analyses.

3. Results

3.1. RS-tDCS participants and sessions

Overall n = 308 participants enrolled in 6 trials for a total of 6,779 sessions (see Table 2), with an average of 23 ± 9.5 sessions (ranging from 10 to 60) completed per participant. Total sessions were 3,137 blinded active, 2,708 sham, and 934 open label active. See Table 2 for a breakdown of assigned conditions, sessions, and montages by trial. The full sample was 70% female with a mean age of 50.26 ± 13.01 [18–78] years; 230 participants (75%) were White, 54 (18%) were African American/Black, 6 (2%) were Asian, and the remaining 15 (5%) were unknown or not reported; 14 (9%) were Hispanic/Latino. Participants were enrolled in clinical trials targeting fatigue, cognitive and/or motor dysfunction due to MS (n = 277) or PD (n = 16), or enrolled in an open-label study targeting symptoms of major depression (n = 3), post-stroke aphasia (n = 3), MS (n = 2), cerebellar ataxia (n = 1), idiopathic hypersomnia (n = 1), chronic pain (n = 1), chronic fatigue syndrome (n = 1), or neurocognitive disorders (n = 3) due to traumatic brain injury (TBI) or mild cognitive impairment (MCI).

For the initial baseline training session, 244 sessions were completed onsite, and 64 were completed remotely (as an accommodation to continue enrollment during COVID-19). Therefore, of the 6,779 total sessions administered, 6,535 RS-tDCS sessions were delivered to the participant at home or another location outside the clinic.

3.2. Tolerability: clearance and session discontinuations

No serious AEs [34] occurred in any of the trials.

Enrollment tolerability testing resulted in n = 1 trial participant of the 308 enrolled (<0.5%) excluded (>7/10 VAS pain rating), resulting in study withdrawal. A total of n = 2 participants were unable to tolerate the target current intensity of 2.0 mA and, per protocol, were lowered to 1.5 mA for the treatment period.

No participant was discontinued due to tolerability after starting the trial. Single session limiting AEs, (defined as VAS rating for pain/discomfort >7) occurred in 27 (0.4%) of all administered sessions (n = 22 participants: 4 blinded active, 10 blinded sham, 8 open label), which resulted in 3 sessions being aborted (n = 3 participants: n = 2 received active tDCS and n = 1 sham tDCS).

No participants were discontinued from the trials because of training or technical difficulties, regardless of whether the initial baseline training was conducted in-person or remotely.

Reported AEs: AE reporting was tabulated by total number of participants, occurrence across total number of sessions, and within participants across sessions (see Table 3). All AEs were reported to be mild to moderate in intensity and did not lead to study discontinuation for any participant. There was no overall difference

Table 2
Summary of total sessions and participants by electrode montage and tDCS condition.

	Blinded Active *#sessions (n participants)*	Sham *#sessions (n participants)*	Open Label *#sessions (n participants)*
Electrode Montage			
DLPFC	2500 (97)	2160 (84)	874 (62)
M1-SO	637 (35)	548 (29)	–
Cerebellar	–	–	60 (1)

in reporting of frequency of tingling, itching and warmth sensation between the checklist reporting and the automated software program (tingling: 75% vs. 60%, $\chi^2 = 2.78$, $p = 0.058$; itching: 45.6% vs. 35.4%, $\chi^2 = 1.39$, $p = 0.388$; warmth sensation: 32.50% vs. 23.9%, $\chi^2 = 2.78$, $p = 0.064$, respectively).

Most Common AEs Reported: The most consistently reported AEs across sessions included tingling (30.7%, 2,084/6,779), warmth sensation (16.3%, 1,106/6,779) and itching (11.9%, 808/6,779). AEs indicated at least once by participants were tingling, warmth sensation and itching: 68% (210/308), 42% (128/308), and 41% (125/308), respectively. Participants with MS did not differ in reporting compared to those with a range of other conditions (within open-label active participants): (72.2% vs. 83.9%, $\chi^2 = 1.99$, $p = 0.159$), itching (36.11% vs. 43.1%, $\chi^2 = 1.23$, $p = 0.266$), and warmth sensation (31.3% vs. 41.9%, $\chi^2 = 0.78$, $p = 0.378$).

Overall, the intensity of these reports was mild (median value on the VAS 0–10: 2.0) and transient in nature (average duration: 4.3 ± 2.1 min). In the blinded trials, there was no difference between blinded active vs. sham in the percent of participants reporting tingling (49.6% vs. 62.3%, $\chi\ 2 = 3.98$, $p = 0.054$), itching (41.6% vs. 53.3%, $\chi^2 = 3.96$, $p = 0.054$) and warmth sensation (29.8% vs. 30.7%, $\chi\ 2 = 0.25$, $p = 0.874$). In the DLPFC 2.0 mA trials, there was a slightly higher rate of reporting of the tingling sensation among participants receiving active stimulation as open-label ($n = 63$) vs. blinded ($n = 97$) (76.2% vs. 50.5%, $\chi^2 = 10.55$, $p = 0.001$).

3.3. Consistency in AE reporting across repeated sessions

Using our two completed double-blinded RCTs, we pooled all participants who received either active or sham tDCS and completed either 20 consecutive sessions of M1-SO tDCS or 30 consecutive sessions of DLPFC tDCS. Itching, tingling, and warmth sensation persisted over time and were consistently reported at each session across both active and sham participants (Fig. 3). There were no significant differences in the proportion of participants who reported tingling (active/sham tDCS: χ^2 (19) = 16.57, $p = 0.619$; χ^2 (19) = 23.21, $p = 0.228$), itching (χ^2 (19) = 25.72, $p = 0.138$; χ^2 (19) = 13.21, $p = 0.828$), and warmth sensation (χ^2 (19) = 21.10, $p = 0.332$; χ^2 (19) = 14.81, $p = 0.735$) across the 20 M1-SO daily tDCS sessions. Similarly, there was no difference in the proportion of participants reporting tingling (active/sham tDCS: χ^2 (29) = 18.24, $p = 0.939$; χ^2 (29) = 23.05, $p = 0.774$), itching (χ^2 (29) = 38.78, $p = 0.109$; χ^2 (29) = 24.19, $p = 0.719$), and warmth sensation (χ^2 (29) = 30.99, $p = 0.366$; χ^2 (29) = 23.56, $p = 0.750$) across 30 DLPFC daily tDCS sessions.

3.4. Other reported AEs

As with the three most commonly reported AEs noted above, no other AEs led to discontinuation (Fig. 4). The frequency of occurrence of other AEs was low (i.e., less than 10%) across the RS-tDCS participants.

3.5. Electrode montage and stimulation intensity

We next tested whether the tDCS montage or current intensity influenced AE reporting rate. To identify any relation between AE occurrence and electrode montage, we analyzed the overall blinded active sessions (DLPFC vs. M1-SO; $n = 97$ and $n = 35$ participants, respectively). We did not find any difference in the percent of participants reporting tingling ($\chi^2 = 0.10$, $p = 0.764$), itching ($\chi^2 = 0.09$, $p = 0.828$), and warmth sensation ($\chi^2 = 2.192$, $p = 0.139$) between DLPFC and M1-SO electrode montages.

To examine AEs by current intensity, we compared the two active blinded DLPFC tDCS conditions of 2.0 mA ($n = 38$ participants) vs. 2.5 mA ($n = 21$ participants). Those receiving 2.5 mA reported slightly higher rates of warmth sensation compared to those receiving 2.0 mA (33.3% vs. 25.7%; $\chi^2 = 4.87$, $p = 0.048$), but no difference in tingling ($\chi^2 = 0.471$, $p = 0.493$) and itching ($\chi^2 = 0.466$, $p = 0.623$).

3.6. Feasibility in class I RCTs

We employed the RS-tDCS protocol to complete two double-blind, sham-controlled RCTs (Table 1), targeting the MS symptoms of fatigue (30 sessions of tDCS paired with cognitive training) and upper extremity impairment (20 sessions of tDCS paired with manual dexterity training). Table 1 shows the demographic and clinical features for each trial. Enrollment of both trials was robust, including during the period of the COVID-19 pandemic, due to the remote access for participation. During April 2019–February 2021 (22 months), we enrolled $n = 120$ participants for the study targeting fatigue. The study targeting upper extremity motor functioning recruited participants with more advanced disability level, with $n = 66$ participants enrolled during April 2018–October 2020 (30 months).

There was a high rate of fidelity to treatment and protocol completion for both studies. In the RCT #1 (NCT03838770),

Table 3
Percentage of participants who endorsed tingling, itching, and warmth sensation in at least one RS-tDCS session broken down by condition (active vs. sham) and electrode montage (DLPFC vs. M1-SO). The table includes only participants with MS.

	DLPFC		M1-SO	
	Active n = 97 participants	Sham n = 84 participants	Active n = 35 participants	Sham n = 29 participants
Tingling, %	50.5	63.1	48.6	66.6
Itching, %	39.1	44.6	45.7	34.4
Warmth Sensation, %	26.8	34.5	38.2	20.0

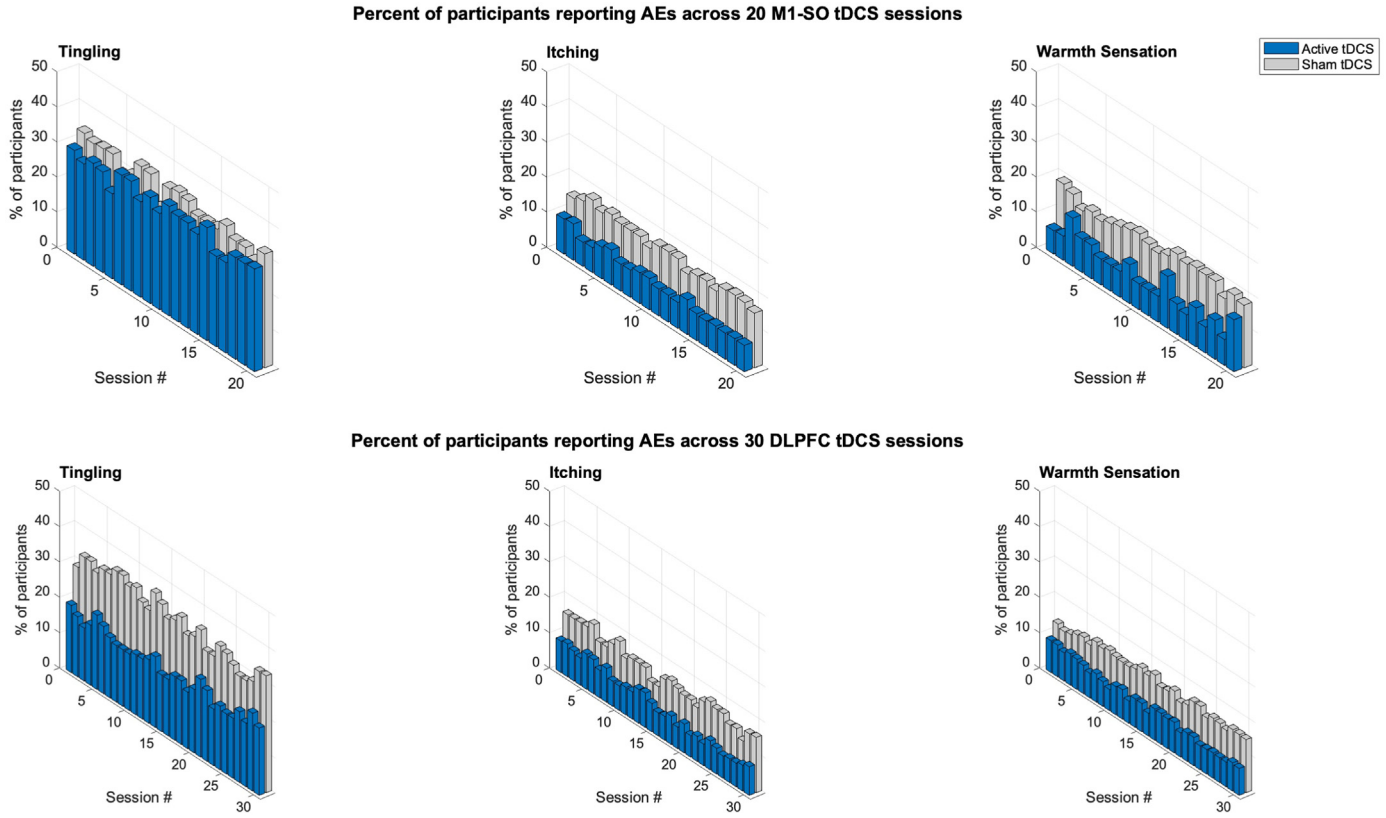

Fig. 3. AE reporting across daily repeated applications. Daily occurrence rate (%) of AEs reported across 30 DLPFC RS-tDCS sessions from n = 54 active and n = 52 sham participants and 20 M1-SO RS-tDCS sessions from n = 34 active and n = 30 sham participants.

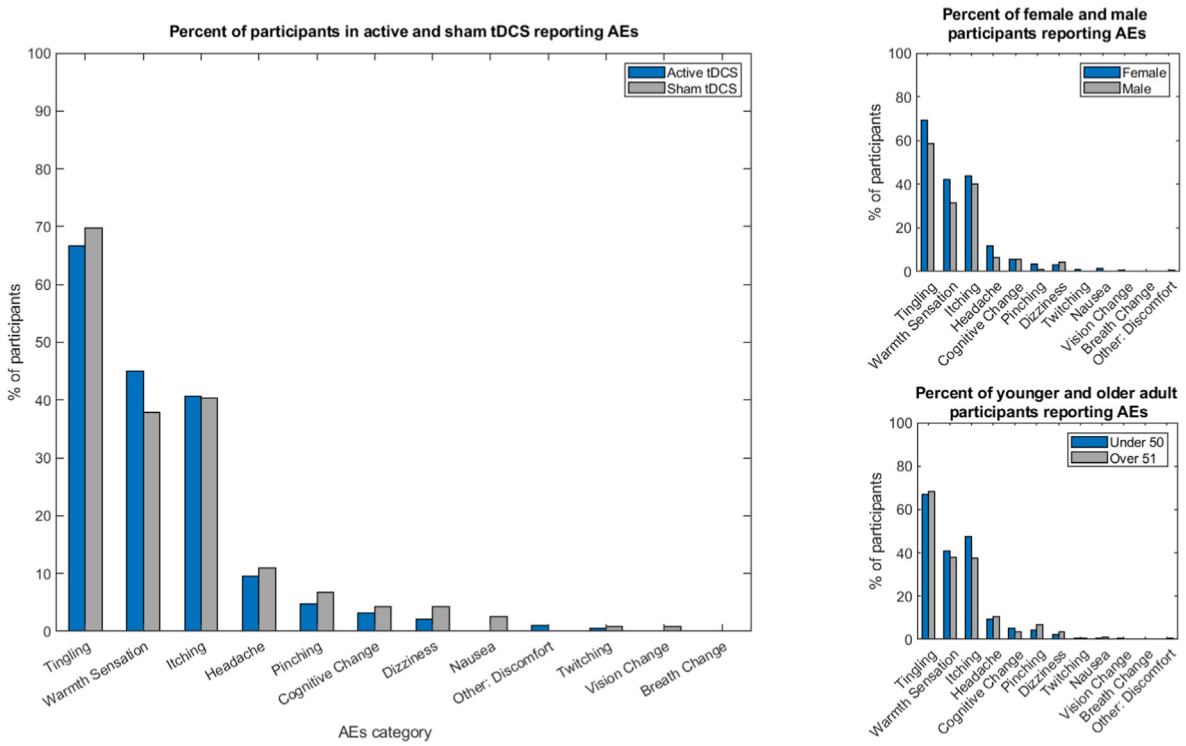

Fig. 4. Other AEs reported. Percentage of participants reporting an AE in one or more sessions by tDCS condition, gender, and age (≤50 years vs. ≥51 years). The active tDCS condition includes blinded and open-label administration. No difference in AE reporting was found among factors (all p's > 0.05).

targeting fatigue and cognition, 92.0% of participants completed 25 or more sessions, with 67.2% participants completing all 30 sessions. In the RCT #2 (NCT03499314), targeting upper extremity motor function, 95% of participants completed all 20 RS-tDCS sessions, with 98% completing at least 18/20.

Both trials met criteria for adequate participant blinding, identifying condition assignment with 53% accuracy for RCT #1 and 36% for RCT #2, both falling within a generally acceptable target of 35–65% [35–37]. The trials differed in montage (M1-SO vs. DLPFC), number of sessions (20 vs. 30), and sham procedure (conventional ramp up/down vs novel three ramp up/down periods). RCT #1 administered 20 M1-SO sessions using the conventional sham of initial ramp up/down period at the beginning, and RCT #2 employed a novel three period ramp up/down procedure. Further, the percent of active and sham participants who accurately guessed whether they received active or sham stimulation did not differ in both RCTs ($\chi^2 = 2.24$, $p = 0.134$; $\chi^2 = 3.22$, $p = 0.073$, respectively).

4. Discussion

Our findings demonstrated the tolerability and feasibility of tDCS delivered to participants at home and over extended time periods in the largest sample reported to date (e.g., up to 60 sessions) [38]. Using the RS-tDCS protocol, tDCS was found to be tolerable and feasible in a diverse range of participants and for repeated applications over time. Our findings extend the established record of safety and tolerability of tDCS [34,39] to include supervised use in the home setting.

Across the 6,779 sessions reported here, the most common AEs were related to the electrode site for both active and sham tDCS: tingling, itching and sensations of warmth. Together, these AEs were commonly reported at each session, were not treatment limiting, and resolved by session completion. In addition, there was no significant change in incidence across repeated exposure, demonstrating the tolerability of tDCS across sessions well beyond the conventional number of sessions (e.g., less than 10 sessions [40]) in the majority of the clinical trials to date. Furthermore, this more extensive exposure did not increase the risk of AEs with repeated application over time (including risk for skin lesion) [41].

Provided rigorous protocols and proper equipment is used [41], our findings are broadly consistent with the tolerability reported for tDCS across the large body of clinical trials to date [1,38,39,42,43], with common AEs being mild (tingling, warmth, itching) and transient. Specific rates of AEs will depend on the exact protocol and equipment utilized. For example, our RS-tDCS reported incidences of head discomfort or pain, including over the cumulative application in our extended protocols, were lower compared to prior reports [33,38,44]. This discrepancy in AE rates may be attributed to our use of specific headsets rather than elastic rubber bands.

Limitations of our analyses include that the majority of our RS-tDCS use to date is in participants living with MS. However, while all have one common diagnosis, the diversity of MS symptom presentation and patient populations provide a robust sample to inform the more generalized use of tDCS for symptomatic or rehabilitative applications. Participants with MS varied across the adult age span, with minimal to more severe levels of cognitive or motor involvement, and a broad range of potential symptoms experienced (e.g., fatigue, pain, and other motor, sensory and mood disturbances).

We used our specific protocol of RS-tDCS for all sessions, including live supervision and a structured paired activity during the stimulation period. While live supervision for all sessions may not be possible for many centers, we believe that our demonstration of its tolerability can allow for participants to be moved to a "briefly supervised" model with live connection for initial "clearance" at the beginning of the daily session versus monitoring throughout the entire session to its completion. While it is clear that live real-time connection with participants at their sessions results in higher treatment fidelity [7], this model of hybrid full and more limited session monitoring has been successfully demonstrated (e.g., Alonzo et al., 2019 [8], Loo et al., 2017 [45]) and enabled by current technology advances.

5. Conclusions

Home-based tDCS is tolerable using the RS-tDCS protocol. The RS-tDCS protocol provides an option to reach larger sample sizes and deliver tDCS over extended treatment periods in RCTs.

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CRediT authorship contribution statement

Giuseppina Pilloni: Conceptualization, Investigation, Data curation, Formal analysis, Visualization, Writing – original draft. **Amy Vogel-Eyny:** Formal analysis, Writing – original draft. **Matthew Lustberg:** Project administration, Data curation, Resources, Writing – review & editing. **Pamela Best:** Data curation, Resources. **Martin Malik:** Data curation, Resources, Writing – review & editing. **Lillian Walton-Masters:** Data curation, Writing – review & editing. **Allan George:** Resources. **Ibraheem Mirza:** Data curation, Resources. **Lana Zhovtis:** Writing – review & editing. **Abhishek Datta:** Writing – review & editing. **Marom Bikson:** Visualization, Writing – review & editing. **Lauren Krupp:** Investigation, Writing – review & editing. **Leigh Charvet:** Conceptualization, Investigation, Funding acquisition, Formal analysis, Visualization, Writing – original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Soterix Medical Inc. provided the tDCS equipment used for research use. The City University of New York holds patents on brain stimulation with MB as inventor. The City University of New York holds patents on brain stimulation with AD as inventor. AD is an employee of Soterix Medical Inc. AD has equity in Soterix Medical Inc.

MB has equity in Soterix Medical Inc. MB consults, received grants, assigned inventions, and/or serves on the SAB of SafeToddles, Boston Scientific, GlaxoSmithKline, Biovisics, Mecta, Lumenis, Halo Neuroscience, Google-X, i-Lumen, Humm, Allergan (Abbvie), Apple.

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