Official Title:	Study of the Combined Effect of Transcranial Direct Current Stimulation (tDCS) and Physical Activity on Gait and Functional Mobility in Participants With Multiple Sclerosis
NCT Number:	NCT03658668
Study Number:	18-00534
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	• September 9, 2020

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Tool Revision History:

Version Number	Version Date	Summary of Revisions Made
6.0	6 AUGUST 2020	- tDCS sessions 2-10 and physical activity to be completed remotely - follow-up visit will occur within 3 days after session 10 and the original 4 week follow-up is optional - Removed i-1MW and i-TUG assessments from sessions 2-10 - Add internet access and adequate space to inclusion criteria - Add T25-FW and Berg Balance scale - Made closed-eyes portion of posturography assessment as optional measure - Add BICAMS cognitive assessment
5.1	16 NOVEMBER 2018	Statistical Analysis of Exploratory Endpoint Study timeline
5.0	23 OCTOBER 2018	Screening process modification Clarification of eligibility criteria Collection of EMR data
4.0	08 AUGUST 2018	Modifications of eligibility criteria
3.0	20 JULY 2018	Specified optional assessments and addition of posturography
2.0	20 JUNE 2018	Added actigraph and EEG assessments
1.0	23 MAY 2018	Initial submission

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A pilot, randomized, double-blind, sham-controlled study of the combined effect of Transcranial Direct Current Stimulation (tDCS) and physical activity on gait and functional mobility in participants with Multiple Sclerosis

Principal Investigator:	Dr. Leigh Charvet, Ph.D Department of Neurology, NYU Langone Medical Center East 38th Street, New York, NY 10016, USA Leigh.Charvet@nyumc.org 646-501-9257
Additional Investigators:	Lauren Krupp, M.D. Director, Multiple Sclerosis Comprehensive Care Center Department of Neurology, NYU Langone Medical Center East 38th Street, New York, NY, 10016, USA Leigh.Charvet@nyumc.org 646-501-7500 Giuseppina Pilloni, PhD Department of Neurology, NYU Langone Health 222 East 41 Street, New York, NY, 10017 (929) 455-5568
NYULMC Study Number:	18-00534
Funding Sponsor:	Not Applicable
IND/IDE Number:	Not Applicable
Regulatory Sponsor:	Not Applicable
Study Product:	Not Applicable
Study Product Provider:	Not Applicable
ClinicalTrials.gov Number	NCT03658668

Initial version: 05/23/18

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Table of Contents

List of Abbreviations

ADL	Activities of Daily Living
AE	Adverse Event/Adverse Experience
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FSS	Fatigue Severity Scale
FWA	Federal Wide Assurance
IRB	Institutional Review Board
i-10MW	Instrumented 10 meter walking
i-TUG	Instrumented Time Up and Go
MS	Multiple Sclerosis
MFIS	Modified form of the Fatigue Impact Scale
MSWS	Multiple Sclerosis Walking Scale
N	Number (typically refers to participants)
NIBS	Non- Invasive Brain Stimulation
PA	Physical Activity
PI	Principal Investigator
pwMS	People With Multiple Sclerosis
RR-MS	Relapsing Remitting Multiple Sclerosis
SP-MS	Secondary Progressive Multiple Sclerosis
tDCS	Transcranial Direct Current Stimulation
US	United States
VAS- F	Visual Analogue Scale Fatigue
VAS- P	Visual Analogue Scale Pain
i-2MWT	Instrumented 2 Minute Walk Test
i-DPAS	Instrumented daily assessment of physical activity and sleep
T25-FW	Timed 25- Foot Walk

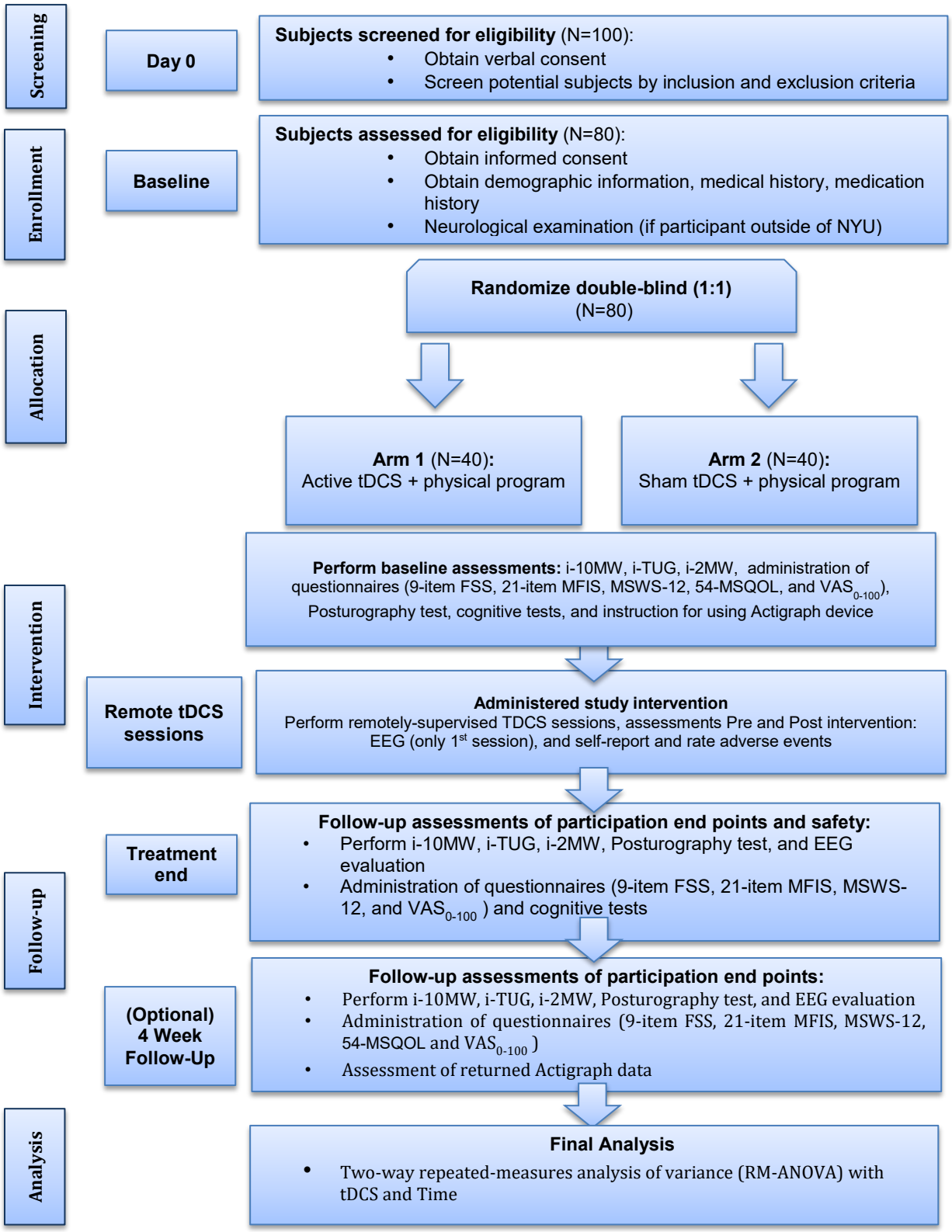
Protocol Summary

Title	A randomized, double-blind, sham-controlled pilot study of the combined effect of Transcranial Direct Current Stimulation (tDCS) and physical activity on gait and functional mobility in participants with Multiple Sclerosis
Short Title	tDCS and physical activity to improve mobility in Multiple Sclerosis
Brief Summary	This study is aimed to test the efficacy of transcranial direct current stimulation (tDCS) combined with a physical activity (PA) program, in 80 individuals affected by Multiple Sclerosis (MS). In particular, this study will evaluate the efficacy of tDCS when administered simultaneously with PA on walking, functional mobility, and fatigue. The subjects enrolled will be randomly assigned to the active group (active tDCS+PA) or the sham group (sham tDCS+PA)
Phase	N/A
Objectives	The primary objective is to determine the efficacy and the feasibility of the combination of the tDCS and Physical Activity (PA) to improve gait performance objectively measured by a 10-meter walk test (i-10MW) using wearable inertial sensors. The secondary objective is to determine the efficacy of tDCS combined with PA to improve functional mobility, brain activation during cognitive test performance, balance, and fatigue.
Methodology	**Study Type:** Interventional **Study Design:** **Allocation**: Randomized **Intervention Model**: Parallel Assignment **Masking**: Double (Participant, Investigator) **Primary Purpose**: Treatment **Estimated Enrollment**: 80
Endpoint	**Primary outcome measures:** • Comparison of change in gait velocity and stride length at baseline and participation end between the active and sham conditions • The number of participants completing the study session (goal: 80% of the participants) **Secondary outcome measures:** • % of remote tDCS sessions completed • Comparison between the active and sham conditions on functional mobility parameters (phase duration of Sit-to-Stand, Stand-to-Sit, Mid and End turning; acceleration and angular velocity) and the Timed Up and Go Task (TUG) • Comparison between the active and sham conditions on EEG signals before and after the first and final tDCS session • Comparison between the active and sham conditions on static balance ability • Comparisons between the active and sham conditions on Fatigue Severity Scale (FSS), 21-item Modified form of the Fatigue Impact Scale, 12-item Multiple Sclerosis Walking Scale, Multiple Sclerosis Quality of Life-54 (MSQOL-54)
Study Duration	Estimated study start date: June 2018 Estimated study end date:

Participant Duration	Approximately 6 hours to 7 hours total over 9 remote sessions plus a baseline and a follow-up visit.
Duration of IP administration	20 minutes of tDCS in each daily session
Population	**Age Eligible for study**: 18 years to 70 years **Sex Eligible for study**: All **Condition**: Multiple Sclerosis
Study Sites	NYU Langone Health, USA
Number of participants	80 participants
Description of Study Agent/Procedure	• Device: Active tDCS tDCS is a therapeutic treatment that utilizes low amplitude direct currents (<4 mA) to induce changes in cortical excitability. Other Name: Soterix 1x1 tDCS mini-CT • Device: Sham tDCS During a sham session, the device is programmed to ramp up to the desired intensity (target 2.5 mA) and ramp down for the initial 60 seconds, with no current delivery during the session, and then again at the end of the session. These brief periods of stimulation serve to mimic the effects of a true stimulation session. • Behavioral: Physical Activity (PA) program consisting of 20 minutes of cycling on an ergonomic cross-trainer.
Reference Therapy	N/A
Key Procedures	20 minutes of tDCS combined with 20 minutes of PA
Statistical Analysis	Two way repeated-measures analysis of variance (ANOVA) with tDCS (active, sham) and Time (baseline, end treatment, 4 week follow-up)

Schematic of Study Design

Flow diagram



1 Key Roles

Principal Investigator
Dr. Leigh Charvet, Ph.D
Department of Neurology, NYU Langone Medical Center
East 38th Street, New York, NY 10016, USA
Leigh.Charvet@nyumc.org

Co-Investigators
Lauren Krupp, M.D.
Director, Multiple Sclerosis Comprehensive Care Center
Departent of Neurology, NYU Langone Medical Center
East 38th Street, New York, NY, 10016, USA
Leigh.Charvet@nyumc.org
646-501-7500

Giuseppina Pilloni, PhD
Department of Neurology, NYU Langone Medical Center
MS Comprehensive Care Clinic
222 East 41st Street, New, York, NY 10017

2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Multiple Sclerosis (MS) is a frequent and common neurological disorder among young adults. Its course is characterized by a progressive neurological deterioration that can cause motor, sensory and cognitive dysfunction. Among the wide spectrum of signs and symptoms, tremor, spasticity, fatigue, and pain often present as well as balance and gait dysfunctions, which can be caused by a combination of fatigue, muscular weakness, and spasticity [Cameron and Wagner, 2011]. Gait alterations, which typically result in reduced speed, decreased step length and alteration of the physiological stance/swing phase duration [LaRocca et al., 2011; Pau et al., 2016; Pau et al., 2017] represent a serious issue for a large portion of people with MS (pwMS) (approximately 40% [LaRocca et al., 2011]) and negatively affects their quality of life. In fact, physical inactivity or sedentary lifestyle is common in patients with MS, and can initiate a cycle of deconditioning and worsening of symptoms [Motl et al. 2005; Motl et al., 2010]. By contrast, physical activity (PA) behavior, particularly exercise training, have beneficial effects on the various processes of MS [White et al., 2008].

Given that MS is a chronic, long-lasting and disabling disease, physical training plays an important role in maintaining an independent lifestyle and good quality of life [Takemasa et al., 1998]. The goal is to minimize functional disability and optimize functional motor recovery. Exercise training, like cycling or treadmill protocol, is a planned, structured, and repetitive PA, and if undertaken over time, can lead to improved physical fitness [Bouchard et al., 1994]. Exercise training has been considered the most effective nonpharmacological treatment in MS with robust evidence for improvements in walking outcomes [Snook et al., 2009; Dalgas et al., 2014; Pearson et al., 2015]. However, current protocols generally achieve only limited recovery of motor impairments [Sutliff et al., 2016]. Thus, there is the need to develop new methods capable of enhancing the effects of rehabilitation therapies.

Recently, considerable attention has been drawn to non-invasive brain stimulation (NIBS) to help the brain to reach an optimal state of activity to facilitate subsequent training effects. Recent studies reported that the

positive effects of physical activities might be potentiated by NIBS and that it has the potential to be considered an adjuvant tool able to enhance the rehabilitation effects.

Transcranial direct current stimulation (tDCS) is a non-invasive treatment option that has been found to reduce the intensity of a wide array of symptoms in neurological disorders such as Parkinson's disease, cerebral palsy, stroke, multiple sclerosis, and depression among others. The effects of tDCS are thought to be mediated through alterations of the resting potential of neurons via distribution of direct electrical current. A mild electrical current (≈2mA) is typically applied through electrodes placed on the scalp. It is a relatively inexpensive treatment modality that has been shown to be safe and tolerable in many clinical populations.

The tDCS method has several advantages [Klooster et al., 2016] over other transcranial stimulation techniques (i.e. repetitive transcranial magnetic stimulation, theta burst stimulation or electroconvulsive therapy), such as easiness of application, affordable cost, lack of lasting or serious side effects, possibility to be delivered remotely [Charvet et al., 2020; Kasschau et al., 2015; Chan et al., 2017], and a superior persisting modulating effect on the cerebral cortex [Woods et al, 2016].

The potential benefits of tDCS vary widely as studies have shown efficacious treatment of symptoms such as pain, fatigue, spasticity, anxiety or depression [Chalah et al., 2015; Hanken et al., 2016; Charvet et al., 2017]. In pwMS active stimulation induces significant pain relief, improvement of muscle strength, and motor dexterity [Meesen et al., 2014; Mori et al., 2010]. Studies, including our own (Charvet et al., 2017), have reported that tDCS improves symptoms of fatigue when compared to sham stimulation with lingering benefit for several weeks following stimulation [Saiote et al., 2014; Chalah et al., 2017]. Beyond symptom management, tDCS has been theorized to improve both cognitive and physical learning processes with the chance for active rehabilitation (REFS).

tDCS has been used to improve physical performance and rehabilitation [Angius et al., 2017; Ferrucci et al., 2016; Sánchez-Kuhn et al., 2017]. In particular, it has recently been reported that the use of tDCS in conjunction with PAsuch as gait training, balance training, and occupational therapy results in significant improvements in motor functions (gait, balance, dexterity and hand task for daily living activity) in both healthy individuals and people with Parkinson disease, cerebral palsy and stroke [Bastani et al., 2012; Elsner et al., 2016; Pixa et al., 2017]. Despite these reports, limited studies have been conducted to improve motor performance in PwMS.

The combination of tDCS and PA has been shown to induce positive changes in gait performance, specifically in regard to stride length, stride length variability, and gait velocity [Kaski et al., 2013; Satow et al, 2016; Yotnuengnit et al., 2017]. Pozzi et al. found that patients with cerebellar ataxia had significant objective and self-rated improvement of symmetrical step execution and reduction of step width (indicating improved gait) following 5 consecutive tDCS sessions [Pozzi et al., 2014].

Based on the theoretical basis of tDCS as well as promising previous evidence, we believe that tDCS is a suitable and favorable complementary technique for motor rehabilitation therapy in MS. This double-blinded, randomized pilot study will pair tDCS (or sham) with PA for 10 sessions to improve motor outcomes. PwMS will be recruited and assigned to either an active or sham (placebo) study condition to assess the efficacy of the tDCS treatment.

2.2 Name and Description of the Investigational Agent

The equipment that will be employed to administer the tDCS stimulation is the Soterix mini-CT.
The Soterix Medical 1x1 tDCS mini- stimulator unit is equipped with:

- Internal rechargeable battery
- Connector port for the anode and cathode cable
- USB charger jack for charging the internal rechargeable battery
- STATUS LCD displays that allows the set-up of administration session (stimulation sequence, dose and time duration)
- Connecting cables (1 Red anode cable and 1 Black cathode cable)

This device is fully programmable and easy to use. It records session data (connection quality, session duration, etc.) for all sessions. The device has built-in safety functions including an automatic abort feature, which ends the session if electrode contact is lost. Sponge pads with rubber electrode inserts (Soterix Easypads) are saturated with saline solution before use to conduct the mild electrical current across the scalp.

2.2.1 Clinical Data to Date

To the best of our knowledge, there is no available clinical research data on the effects of the combination of tDCS and simultaneously performed PA in pwMS. However, PA has been proposed as a useful and effective approach to improving some of the most typical motor impairments caused by MS [Motl et al., 2005; Motl, 2010].

The most promising results, published for the improvement of motor performances, are on hand dexterity wherein tDCS was applied alone or in association with motor training [Iodice et al., 2017]. There is positive outcome data from other clinical trials conducted in patients with neurologic diseases with impaired mobility including modulation of cortical excitability and enhanced motor skill learning, locomotion, and balance [Iodice et al., 2017, Kaski et al., 2013, Pozzi et al., 2014].

Our lab has conducted multiple tDCS trials to date, with two active IRB protocols through NYU Langone Health. We have conducted over 2000 sessions of tDCS paired with cognitive remediation with extremely high tolerability and feasibility (>99%). We have positive clinical outcomes with statistically significant improvement of cognitive processes and reduction in fatigue in pwMS.

2.2.2 Dose Rationale

tDCS does not induce direct activation of the neural action potential because the electrical current (typically in the 0.5–4.0 mA range) does not depolarize the neuron to the threshold firing potential [Nitsche et al., 2007; Nitsche et al., 2008]. However, tDCS modifies the transmembrane neuron potential and thus influences the level of the cortical excitability [Wagner et al., 2007]. In clinical research, the employed current typically ranges from 1 to 2.5 mA across a 20 cm^2 electrode. This configuration has been proven to be the safest maximum level tolerable [Brunoni et al., 2012]. For this study we will be applying a maximum of 2.5 mA of current across a 20 cm^2 electrode for 20 minutes per session.

2.3 Rationale

Multiple Sclerosis (MS) is a progressive neurological disorder that represents the most common cause of disability in young subjects [Haussleiter et al., 2009]. The course of MS is characterized by a progressive deterioration due to the accumulation of several neurological dysfunctions [Cameron and Wagner, 2011] including motor deficit, sensory dysfunction, and sphincter disorders, which greatly impact the quality of life of the affected person. In particular, MS affects individuals during their most productive years decreasing their physical abilities and thus causing difficulties in functional mobility, walking and performance of activities of daily living (ADL).

PwMS often undergo motor rehabilitation programs to reduce muscle tightness, prevent joint stiffness, improve muscle strength and correct postural instability and gait abnormalities. In particular, current gait rehabilitation strategies for pwMS include repetitive adaptive physical activity, walking training, treadmill training, the use of orthoses and functional electrical stimulation [White et al., 2004; DeBolt et al., 2004; Pedersen et al., 2006; Snook et al., 2009; Pau et al., 2017].

However, recent studies have reported that the positive effects of PA might be potentiated by non-invasive brain stimulation, which can be considered to act as a catalyst that enhances the rehabilitation effects. tDCS is a technique that uses low amplitude direct currents to modify cortical excitability. With well-established safety, tolerability, and ease of administration, tDCS has been found to have the potential to ameliorate symptoms such as depression and pain in a range of conditions as well as to enhance outcomes of cognitive and physical training.

Previous studies suggest that tDCS, modifying cortical excitability, may prime or prepare the cortex for subsequent training and furthermore, may improve overall functional outcomes [Webster et al, 2006; Brown & Pilitsis, 2006]. Hence, the working hypothesis of this pilot study is that the simultaneous administration of tDCS and physical activity training (using a cycling protocol) enhances lower limb functionality, expressed in terms of improved gait and functional mobility performance, by reinforcing synaptic connections within networks of motor cortex.

In summary, this study aims to test the efficacy of tDCS combined with a PA program to evaluate the capability of such approach in improving gait and functional mobility. In addition, this study will adopt our established and validated remotely-supervised tDCS (RS-tDCS) protocol (Charvet et al., 2020) to evaluate the feasibility to deliver at-home a structured and supervised PA program paired with tDCS.

The design is a randomized, double-blind, sham-controlled study. Participants will be selected among individuals with a clinically established diagnosis of MS suffering from relapsing-remitting form, with a disability level (expressed through the Expanded Disability Status Scale, EDSS) compatible with the performance of the physical activity program (EDSS Score less than 6.5).

Participants assigned to the control group will be subjected to “sham” stimulation protocol, which encompasses an initial ramping stimulation up and down like in the real stimulation condition, but limited to the first and last minute of stimulation. In this way, even though subjects will perceive the initial itching/tingling sensation, the stimulation duration will be too short to induce after-effects. By comparing the results in individuals exposed to sham stimulation with the results of subjects exposed to anodal stimulation, it will be possible to assess whether the effect of tDCS combined PA is caused by the current stimulation, rather than by the placebo effect. No additional risks are associated with the control group and for this reason no particular restrictions are required for the randomization of eligible participants in the two arms of the study.

In regards to the stimulation parameters, previous studies were characterized by many different variables such as: intensity of current, duration of each session, and total number of sessions. However, in clinical research, intensities ranging from 1 to 4 mA are typically used with a 20 cm^2 electrode since this setup has been proven to be the safest maximum level that can be used [Woods et al., 2016; Nitsche and Paulus, ed2000; Nitsche et al. 2003]. The protocol design is defined according to the purpose of the study. For the induction of relevantly longer-lasting tDCS effects, spaced stimulation with intervals ≤ 30 min is suitable [Monte-Silva et al. 2013b; Goldsworthy et al. 2014].

In terms of protocol design, there will be 10 consecutive days of anodal stimulation (anodal electrode attached at Cz position, along with a cathodal electrode will be attached at the supraorbital area on the forehead), paired with simultaneously physical therapy for 20 minutes as was found to be effective in motor cortex neuromodulation [Kaski et al., 2013; Fleming et al., 2016].

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

The application of tDCS is associated with low risks as reported by previous clinical and research studies [Bikson et al., 2016; Woods et al., 2016]. The most common side effects of tDCS are classified to be mild, benign, short-lived, and the rates of common adverse effects did not differ between the active arms of the studies and the sham arms [Bikson et al., 2016].

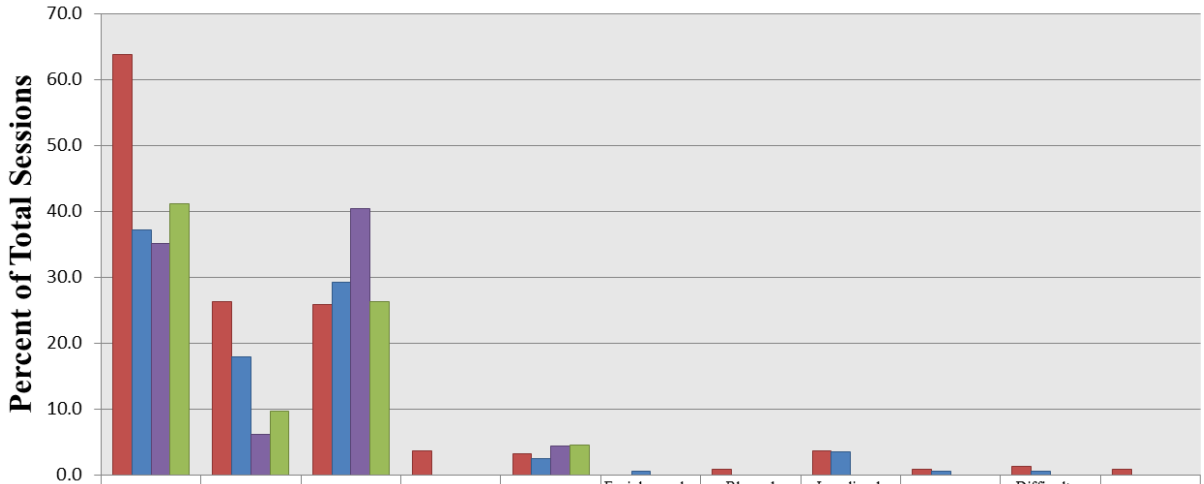
The most immediate safety risk for tDCS is the potential for mild irritation resulting from tingling, itching, or warmth/burning sensations during and immediately following treatments. However, risk to subject has been substantially ameliorated through the implementation of several aforementioned recommendations (included in the exclusion criteria), and standard parameters.

Standard parameters to date indicates that the current is less than 5 mA, it is applied through electrodes that are known to minimize skin burns at the specific current level (i.e. wet saline electrodes as used in this protocol), the current application duration is less than 20-60 min per session, and that the sessions are not more frequent

than twice per day.

The most common adverse events (AE) of tDCS are [Brunoni et al., 2011]: itching (39.3%), tingling (22.2%), headache (14.8%), burning sensation (8.7%), and discomfort (10.4%). Based on our extensive use in previous studies a physical burn or lesion has never occurred. The following figure (Fig. 1) displays adverse events reported through our previous studies. AE rates were largely on par with those reported in the literature to date.

Figure 1: Adverse Events experienced with tDCS



	Tingling	Itching	Skin Burning	Nausea	Headache	Facial muscle twitching	Blurred vision	Localized head pain	Forgetfulness	Difficulty concentrating	Dizziness
1.5mA OL	63.7	26.2	25.8	3.6	3.2	0.0	0.8	3.6	0.8	1.2	0.8
2.0mA BL	37.1	17.8	29.2	0.0	2.5	0.5	0.0	3.5	0.5	0.5	0.0
2.0mA OL	35.1	6.1	40.4	0.0	4.4	0.0	0.0	0.0	0.0	0.0	0.0
Sham	41.1	9.7	26.3	0.0	4.6	0.0	0.0	0.0	0.0	0.0	0.0

Risks associated with the PA program are limited to mild risks from cycling including potentially uncomfortable physical exertion and increased heartrate.

2.4.1.1 Risks of Cubii Under-Desk Elliptical

Cubii elliptical is associated with minimal risks, limited primarily to proper set-up, usage, and maintenance of the equipment. These risks include: (1) utilizing the Cubii on a non-level surface; (2) utilizing the Cubii while standing; (3) utilization of a chair with unlocked wheels; and (4) improper securing of the pedals. Prior to each study session, participant safety per the aforementioned safety checks will be assessed by the study technician.

2.4.2 Known Potential Benefits

Previous research on the use of tDCS in pwMS reported a range of immediate potential benefits such as:

- Improvement in cognitive functioning and working memory [Charvet et al., 2017]
- Reduction in depression symptoms and fatigue [Ferrucci et al., 2014; Saiote et al., 2014; Charvet et al., 2017]
- Reduction in pain and anxiety [Mori et al., 2010]

The long-term potential benefits of repeated applications of tDCS, their interaction with specific learning stages and tasks and the extent to which these performance improvements are retained in the long term remain to be addressed.

The use of our established RS-tDCS protocol can improve access to physical activity programs, increase the engagement and remove the barriers of time and travel to clinic appointments (Shaw et al., 2019; Charvet et al., 2020).

3 Objectives and Purpose

In pwMS comparing those receiving active stimulation versus those receiving sham stimulation, the objectives are as follows:

3.1 Primary Objective

- To determine the efficacy and the feasibility of the combination of the tDCS and PA to improve gait performance objectively assessed using wearable inertial sensors previously validated for use in pwMS (Pau et al., 2016; 2017).

3.2 Secondary Objectives

- To determine the feasibility of delivering at-home a structured and supervised PA program paired with tDCS
- To evaluate changes in functional mobility after tDCS and PA treatment by instrumented Time Up and Go (i-TUG) performed using wearable inertial sensors at baseline, and at 4-week.
- To evaluate change in non-motor symptoms such as general perceived fatigue, cognitive and psychological aspects
- To evaluate safety and tolerability by assessing both experiences of minor adverse events and pain ratings
- To evaluate changes in level of daily physical activity and sleep as assessed by the ActiGraph device (optional)
- To collect pilot data on tDCS-related changes in brain activity as measured by 3-electrodes frontal EEG sensor (optional)
- To evaluate changes in standing balance measures provided by static Posturography test

Study Design and Endpoints

3.3 Description of Study Design

This is an interventional, randomized, double-blind (participant and study staff), sham-controlled, parallel design, pilot study of N=80 RR-MS and SP-MS participants, characterized by mild to moderate gait dysfunctions. There will be a 1:1 random assignment of participants to receive either the active or the sham tDCS while performing the PA program. Blocked stratification will be used to randomize the participants to their respective study conditions. Block sizes of 4 and 6 will be used and the stratifying factor will be EDSS score (0-3.5 and 4.0-6.5). Randomization will be done by an independent randomizer who takes no part in baseline, follow-up, or sessions to maintain the double-blind nature of the study.

3.4 Study Endpoints

3.4.1 Primary Study Endpoints

To determine the efficacy of the combination of tDCS and physical training, the following primary outcome measures have been chosen**:**

- Efficacy measured by comparison between the active and sham conditions by comparing the changes in gait velocity and stride length at baseline and participation end
- Compliance measured by 80% of participants having completed the study sessions

3.4.2 Secondary Study Endpoints

- The feasibility of delivering at-home supervised PA paired with tDCS will be assessed using the number of completed sessions at-home. It will be considered as "feasible" when participant complete successfully at least 80% of the total at-home sessions
- Comparisons between the active and sham conditions at baseline and at the end of the study by assessing the changes in gait spatial-temporal parameters (stance, swing and double support phase; cadence; step width) and functional mobility parameters objectively assessed using wearable inertial sensors
- Comparisons between the active and sham conditions at baseline and participation end conditions by assessing the changes in scores of 9-item FSS (physical aspect of fatigue) and 21-item MFIS (physical 9 items, cognitive 10 items, psychosocial 2 items), MSWS-12 (subjective measures of impact for walking ability and related pathology), and MSQOL-54 (36 items for generic health-related quality of life measures and 18 items for MS-specific measures).
- Comparisons between the active and sham conditions at baseline and participation end conditions by assessing the changes in scores of VAS- $F_{0\text{-}10}$ (to assess the perceived general fatigue)
- Review of experiences of minor adverse events and pain ratings. In particular, participants will have to report and rate any adverse events. Pain ratings will be measured, using a VAS- $P_{0\text{-}10}$ (rating 1 for minimal to 10 for most severe), before and after each session (any experience of pain or other adverse event above an intensity rating of 7 will result in study discontinuation)
- Comparisons between the active and sham conditions at pre and post tDCS-PA session by assessing the changes in the performance of the cognitive tests and EEG signal changes during the time of testing
- Comparisons between the active and sham conditions at baseline and participation end conditions by monitoring the changes in level of daily physical activity and amount of sleep as measured by ActiGraph
- Comparisons between the active and sham conditions at baseline and participation end conditions by monitoring the changes in sway parameters as objectively measured by the instrumented Posturography test and by monitoring changes in total score Berg Balance Scale.
- Change in processing speed between baseline and immediately after the treatment end to assess improvement in cognitive function as indirect effect of aerobic PA.

3.4.3 Exploratory Study Endpoint

As an optional measure, we will collect participants' electronic medical records, including MRI brain scans already collected during previous clinical visits, to evaluate whether there is a correlation between the degree of brain atrophy and the participants' clinical response to tDCS i.e., the level of improvement in gait, balance and cognitive measures after tDCS treatment. Previous studies showed inter-individual variability in response to tDCS treatment. One of the factors that affects biological response to electrical current was shown to be the degree of brain atrophy [Lucia et al., 2015; Mahdavi et al., 2018]. Recent studies based on human head model showed how brain characteristics such as total brain and grey matter volume can perturb the current distribution density throughout the brain [Mahdavi et al., 2018]. Specifically, reduced grey matter volume was associated with low magnitude of current density in the brain.

4 Study Enrollment and Withdrawal

4.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Age 18-70
2. Definite MS diagnosis, subtype relapsing-remitting (RR-MS) or secondary-progressive (SP-MS)
3. Expanded Disability Status Scale (EDSS) from 1 to 6.5 with clinically significant gait deviations
4. Clinically stable

5. Able to independently walk with or without an assisting device (i.e. cane, crutches or walking frames) for medium-long distance
6. Absence of other associated medical conditions that would prevent participants from performing physical activity, such as cardiorespiratory and severe osteoarticular disorders
7. Able to use study equipment
8. Able to commit to 10 sessions of tDCS while performing physical program with baseline and follow-up visits
9. Able to understand the informed consent process and provide consent to participate in the study
10. Stable and continuous access to internet service at home
11. Adequate home facilities (enough space, access to quiet and distraction free area)

4.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Visual, auditory and motor deficits that would prevent full ability to understand study, as judged by treating neurologist or study staff
2. Primary psychiatric disorder that would influence ability to participate
3. Receiving current treatment for epilepsy
4. Uncontrolled headaches and 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
5. 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)
6. 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)
7. Treatment for a communicable skin disorder currently or over the past 12 months
8. History of uncontrolled or labile hypertension
9. Other serious uncontrolled medical condition (e.g. cancer or acute myocardial infarction)
10. Wide Range Achievement Test-4th Edition (WRAT-4) Reading Recognition scaled score < 85
11. History of clinically significant abnormalities on electrocardiogram (EKG)
12. Presence of chronic medical illness and/or severe ataxia
13. Botulinum toxin injection within the past 4 months
14. Functional surgery for lower limb in the past 6 months (e.g. hip or knee replacement)
15. Alcohol or other substance use disorder
16. Pregnant or breastfeeding

4.3 Strategies for Recruitment and Retention

The MS Comprehensive Care Center of NYU Langone Medical Center has an extensive recruitment base. Patients will be recruited to participate in studies from all over New York and the other regions within the continental United States. Patients who are seen by medical staff at NYU Langone Medical Center, who fit the eligibility criteria, will be referred for the study by the study PI and sub-investigators. All physicians and medical staff at the MS Care Center will be presented with the study description.

A patient who is seeing one of these medical staff members as their treating physician will be introduced to the study by that medical staff member. If the patient is interested and agrees to be contacted by the study team, then a member of the study staff will contact them. Once a patient is identified, study staff will meet with the patient or call them to provide additional information regarding study participation. After the patient has reviewed

the consent form and asked all questions, and provides consent to participate, the patient will be enrolled in the study.

Advertisements:
An IRB approved flyer will be posted in local physician offices and waiting rooms and throughout NYU, the surrounding community, and on Long Island. A description of the study will be posted on MS related websites

4.4 Duration of Study Participation

Participants will complete study activities for approximately 5 to 7 hours total over the course of 10 sessions.

> The baseline visit will last approximately 1.5-2 hours (30 minutes to consent, 60 minutes for baseline measures and 20 minutes for tDCS session 1) minutes where initial study measures are administered.

At the baseline visit, participants may be provided with a wristwatch accelerometer ActiGraph. They will be asked to wear the ActiGraph wristwatch for the entire study duration until the follow-up visit, except for during water-related events such as bathing, showing and swimming. The first tDCS and PA session will be schedule from 4 to 7 days after the baseline visit. During this window of time (baseline to first study session), participants daily activity will be recorded through the ActiGraph wristwatch. Due to the limited availability of study actigraph devices, use of the ActiGraph will be optional and at the discretion of study staff If the Actigraph is not being used then the first session will occur same day as baseline.

> Remote study sessions 2 through 10 will be approximately 20 minutes in duration, as follows: 20 min: tDCS (active or sham) session while performing PA program lasts 20 min (cycling paired with simultaneous tDCS)

*** Please note that while 10 sessions will be scheduled consecutively across a two-week period, the participant will be able to complete any missed sessions during the 3rd week.**

> Follow-up (Visit 11) will take approximately 1 hour to repeat baseline measures.

> A final follow-up visit will be approximately 1 hour after around four weeks from the end of the treatment. Participants will return the wristwatch accelerometer (ActiGraph) at the follow-up visit and complete gait assessment and self-reported questionnaires.

	Gait and Balance assessment and self-report questionnaires	Gait, Balance, and Functional mobility Measures	EEG with Cognitive Testing*	tDCS (active or sham) + PA	Actigraph Wristwatch Assigned*	Actigraph Baseline*	Actigraph Wristwatch Returned*
Baseline	x				X*	X*	
Session 1		x	x*	x			
Session 2		x		x			
Session 3		x		x			
Session 4		x		x			
Session 5		x		x			
Session 6		x		x			
Session 7		x		x			
Session 8		x		x			
Session 9		x	x*	x			
Session 10	x			x			
Treatment-End Visit	x		x*				x*
Follow-up (4 weeks ± 1 week post-	x*						

Session 10)-Optional							
An asterisk next to a measure indicates that it is an optional assessment that may be foregone in the case of limited time and/or limited availability of the ActiGraph Wristwatch device							

4.5 Total Number of Participants and Sites

Recruitment will end when approximately N=80 participants are enrolled. A 10% potential dropout rate will leave an approximate total of N=72 evaluable participants for the study (refer to sample size estimation).

4.6 Participant Withdrawal or Termination

4.6.1 Reasons for Withdrawal or Termination

Participants are free to withdraw at any time upon request as participation is completely voluntary.

The study site's Investigator can request a withdrawal.
An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

Explicit subject stop criteria have been uploaded as a supporting document.

4.6.2 Handling of Participant Withdrawals or Termination

If a participant wishes to withdraw from the study they may do so at any point. The participant can be contacted by e-mail, telephone or other minimum-level contact.

4.7 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Leigh Charvet. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements

Study may resume once concerns about safety, protocol compliance are addressed and satisfy IRB.

4.8 Study Behavioral Intervention

To date, despite significant progress in the development of disease-modifying drugs, pharmacologic therapy alone does not warrant optimal care in pwMS. In fact, exercise has been recognized as a feasible form of self-management for people with disease [White et al, 2004]. Regular exercise can improve daily activity, cardiovascular fitness, muscle strength, health perception, and fatigue indices in pwMS [Motl et al., 2012]. For these reasons, physical activity has been used and recommended in pwMS to reduce muscle tightness, prevent joint stiffness, correct postural instability, and gait abnormalities. Cycling and walking training share similar locomotor patterns of reciprocal flexion and extensions movements and have alternating muscle activation of antagonists, and they are the most used physical exercise in rehabilitation settings.

4.8.1 Administration of Intervention

Physical activity program based on cross-trainer machine

Participants will perform the aerobic exercise-conditioning program with the use of an ergonomic cross-trainer for 20 minutes while receiving concurrent tDCS. During the cycling protocol, participant will maintain a level of perceived exertion between 5 and 8 (Hard and Really Hard) on Borg Scale (Halabchi et al., 2017). The assessment of perceived exertion will make sure that participant will train safely at the correct intensity to achieve physical benefits for the PA program. Borg Scale will be administered by the study technician every 5 minutes during the 20-minutes exercise training.

4.9 Study Procedural Intervention Description

4.9.1 Administration of Procedural Intervention

Study technicians trained to oversee tDCS sessions will administer the tDCS treatments. Training includes familiarity with the device and all of its safety features. Furthermore, technicians will be trained to properly oversee the physical activity sessions to ensure a safe environment.

Procedure for the administration of the treatment:
Electrodes preparation: the 5 × 5 cm^2 carbon rubber electrodes work with saline solution in order to increase conductance. Inject 5 ml of saline solution on the external surface of the carbon rubber of each electrode.

Electrodes montage: The carbon rubber sponge electrodes will be placed according to the International 10-20 EEG System. The anodal electrode will be attached at Cz position on the scalp, which corresponds to the lower limb motor cortex. The cathodal electrode will be attached at the supraorbital area on the forehead. Before starting stimulation session check the impedance. Study technicians will troubleshoot the connection if the impedance is high enough that the device cannot reliably stimulate.

Arm 1: Active tDCS and physical training
Participants will receive active tDCS while performing physical training (see detailed description in Section 6.3). A direct current of 2.5 mA will be applied throughout the stimulation session.

Arm 2: Sham tDCS and physical training
Participants will receive a sham tDCS while performing physical training (see detailed description in Section 6.3). During a sham session, the device is programmed to ramp up to the desired intensity (target 2.5 mA) and ramp down for the initial 60 seconds, with no current delivery during the session, and then again at the end of the session. These brief periods of stimulation serve to mimic the effects of a true stimulation session.

Schedule of the intervention procedure: 20 minutes of active/sham stimulation, once daily, scheduled for 10 business days over the course of approximately two weeks. The participant will be able to compensate for any missed session the week after to complete a total of 10 visits. The total duration of the treatment will be approximately 3.3 hours (20 mins x 10 sessions).

4.9.2 Remotely-Supervised tDCS Sessions

Following procedures for our validated protocol [25, 69], participants will receive training on the use of the study tDCS device and preconfigured laptop computer. Participants will be given a study laptop computer which will be configured with VSee[67] and TeamViewer[68]. VSee is a HIPAA compliant teleconferencing video software that encrypts data before sending, creating a secure connection between two computers. TeamViewer is a HIPAA compliant program for remote access to directly provide technical support. A tDCS kit will be provided for the participant to take home which will include the tDCS device, tDCS headset, and the one-time use sponge pockets for electrodes. The Cubii will be shipped to the participant's address.

The remotely-supervised sessions will be administered by study technicians who will be connected live with participants via the study provided laptop when initiating and delivering the treatment and can address and document any safety concerns that arise during treatment. The tDCS device is pre-programmed with a single-use unlock codes that must be entered each day in order for the stimulation to begin. The code will be provided by the study technician each day after the participant meets all safety checkpoints. Study technicians will direct headset placement remotely and will observe the patient for duration of the session in real-time. The technicians

are IRB approved study team members who completed CITI, HIPAA, and study-specific training in tDCS, Vsee, and Team Viewer.

If the participant wishes to discontinue the session at any time, they will be instructed to press the "abort" key, which ramps down and ceases the stimulation current within 30 seconds and afterwards permits headset removal.

At each treatment session, participants will complete brief adverse event reports before and after treatment.

Figure 1: Example of RS-tDCS equipment and setup

4.9.3 Assessment of Participant Compliance with Study Procedural Intervention

Participant's compliance to the intervention will be assessed with successful compliance being completion of more than 80% of the assigned sessions. Aborted sessions will be counted as unsuccessful or incompliant sessions.

5 Study Procedures and Schedule

5.1 Study Locations

- 240 East 38th Street, Ambulatory Care Center
- 222 East 41st Street

5.2 Study Procedures/Evaluations

5.2.1 Study Specific Procedures

- **Instrumented 10 meter walking (i-10MW)**
  This test will be used to assess participants' walking ability. The use of a wearable inertial sensor allows for a quantitative measurement of the main spatio-temporal parameters (i.e. speed, stride length, cadence, stance, swing and double support phase duration)

  i-10MW procedure
  The experimental test will be performed in a clinical setting. The participants will be instructed to walk along a 10-meter hallway at their self-selected speed and natural gait. The inertial sensor will be attached at the lower lumbar level (centered on the L4-L5 intervertebral disc) with a semi-elastic belt. The device receives acceleration signals, which are transmitted in real time via Bluetooth to a PC.

  Instrumented 2 Minute Walk Test (i-2MWT)
  This test will be used to assess participants' physical endurance - with the same reliability of the 6MWT (Gijbels, 2011). The objective of this test is to walk as far as possible for 2 minutes, without running or jogging.

i-2MWT procedure
Participants can slow down, stop and rest as necessary, but resume walking as soon as they are able. The experimental test will be performed in a clinical setting. The participants will be instructed to walk, at maximal effort, back and forth in 30-meter (100-ft) hallway turning around cones for 2 minutes and will be permitted to use their habitual assistive devices. The inertial sensor will be attached at the lower lumbar level (centered on the L4-L5 intervertebral disc) with a semi-elastic belt. The device acquires acceleration signals, which are transmitted in real time via Bluetooth to a PC.
Device:
Wireless inertial sensor device G-sensor (BTS Bioengineering S.p.A., ITALY).
The wearable unit includes a tri-axial accelerometer, a gyroscope, and magnetometer.

- **Instrumented Time Up and Go (i-TUG)**
  This test will be used to assess participants' functional mobility. The use of inertial sensor unite introduces a quantitative approach to motion analysis.

  i-TUG procedure
  The experimental test will be performed in a clinical setting with the participants will be instructed to sit on a standard office chair with a back support. Following a verbal signal, participants stand up, walk straight for 3 meters at a comfortable and safe speed [Podsiadlo et al., 1991], perform a 180° turn around a cone, walk back to the chair, and perform a second 180° turn to sit down**.**
  The inertial sensor will be attached at the lower lumbar level (positioned at the center at the L4-L5 intervertebral disc level) with a semi-elastic belt. The device acquires acceleration and angular velocity signals, which are transmitted in real time via Bluetooth to a PC.
  Participants will repeat the test twice: the first trial serves mainly for familiarization, while the second is actually measured and the resulting data will be processed.
  Device:
  Wireless inertial sensor device G-sensor (BTS Bioengineering S.p.A., ITALY).
  The wearable unit includes a tri-axial accelerometer, a gyroscope, and magnetometer.

- **Electroencephalogram** (EEG) **evaluation paired with cognitive testing (Optional)**
  Participants may be asked to wear a miniature 3-electrode head strap device at the discretion of the study staff before and after the first and final tDCS session. The EEG measures the electrical activity in the brain and quantifies and assesses the effect of tDCS intervention. EEG signal analysis may introduce a novel approach in quantifying measurements associated with cognitive load, emotional states, stress, and pain.
  During the EEG measurement period, participants will complete testing using the Cogstate Brief Battery, a validated computer-based platform{CogState, 2015 #95}{Maruff, 2013 #96}{Charvet, 2018 #462} that takes approximately 10 minutes to compute, and the Symbol Digits Modalities Test (SDMT) , a 90 second paper and pencil measure of symbol to number matching.{Smith, 1982 #82}{Charvet LE, 2014 #390}
  Device:
  Functional Brain Activity Sensor (fBAS ™) is a sticker-size, sticker-thin, wireless sensor (medical grade accuracy) that uses three EEG electrodes (Neurosteər, LTD). fBAS device comprises of a EEG sensor and a Bluetooth transmitter. EEG recordings are collected by 3 medical grade electrodes on via a forehead patch, and the captured signals are sent via low energy Bluetooth to a PC for the real-time processing.

  The EEG paired with Cognitive test assessment will be an optional measurement and will be at the study staff discretion when to perform these tests (limited time and/or limited availability of fBAS device).

- **ActiGraph Evaluation (Instrumented daily assessment of physical activity and sleep, i-DPAS)**

  Actigraphy testing involves the use of a portable device called an actimeter which is worn as a wristwatch that records the participant's daily routine movements over extended periods of time (days and nights) except when he/she is bathing or swimming. An Actigraphic device is worn on the wrist and includes several types of sensors to record movement, and the absence of movement for a given

continuous period of time is considered as sleeping. At the end of the test period, the data from the device is downloaded to a computer for analysis using software programs to extract a number of parameters that suggest sleep and wake cycles. The use of the wristwatch device allows quantitative measurement of the participant's daily activity (based on Vector Magnitude and number of steps taken), the intensity of physical activity and hours of sleep.

i-DPSA procedure (Optional)
The participants may be asked to wear a wristwatch sensor- depends on the availability of the device- for the entire duration of the study, from the baseline visit to the follow-up visit in which the data will be collected all throughout. The participants will be instructed to wear the wirstwatch sensor each day for the entire duration of the study on the wrist of non-dominant arm (it is considered to be less intrusive especially during sleep). Participants will return the device at the follow-up visit.
Device:
Tri-axial accelerometers ActiGraph wGT3X-BT (Actigraph ,Pensacola, FL), previously validated for pwMS (Motl et al., 2009).

The monitoring of daily activity with Actigraph will be optional measurement and will be at the study staff discretion when to perform this test (limited time and/or limited availability of the ActiGraph device).

- **Static posturography Test**
  This test will be used to assess participants' static balance ability. The use of static force platform unite introduces a quantitative approach to the evaluation of balance and allow to compute the positions of the centre of pressure (COP) on the ground (this is estimated as compatible with the centre of gravity at about 97%). The COP will be used to calculate the following time domain measures: velocity of the COP on the anteroposterior (AP) or mediolateral (ML) axes (COP vel), the sum of the displacements of COP on the force platform (COP path), and the 95% confidence ellipse area
  (COP area).

  Static posturography procedure
  Static posturography will be performed according to a standardized procedure as follows:
  Each participant will be asked to stand barefoot on the force platform, in upright static condition, double-leg stance, and with arms resting at their sides. The position of the feet on the force-platform is standardized, their feet will be placed on two 30°-oriented footprints (inter-malleolar distance 8 cm) drawn on a paper sheet placed on the force platform. Stance conditions are tested with open eyes (OE) and closed eyes (CE). Each test will be performed 2-3 times based on the ability of each participant and lasts around 30 seconds. The closed eyes static posturography will be an optional assessment depending on the level of impairment of the participant.
  Device: Wii Balance Board (Nintendo) paired via Bluetooth device with a PC. It was previously validated for healthy controls and pwMS (Park and Lee, 2014, Pau et al., 2015, Pau et al., 2017).

- **Timed 25-Foot Walk (T25-FW):** it is a clinical tool that evaluates participants for quantitative mobility and leg function performance test in a timed, 25 foot walk. The scoring for the Timed 25-Foot Walk is the average of two trials.
  T25-FW procedure: the patient is directed to walk 25 feet quickly and safely as possible. Participant can use the assistive devices while doing this task.

- **Cognitive Assessment**
  Brief International Cognitive Assessment in MS (BICAMS) (Benedict et al., 2016): this battery includes tests of mental processing speed and memory. Specifically, it includes the Brief Visiospatial Memory Test (BVMT), Symbol Digit Modality Test (SDMT), and Rey Auditory Verbal Learning Test (RVLT).
  Cogstate Brief Battery (Maruff et al., 2009): brief, computer-administered cognitive test battery that requires approximately 10 minutes for administration and consists of four cognitive tasks that measure psychomotor function, attention, working memory and memory.

- **Balance Clinical Scale**
  Berg Balance Scale (Berg et al., 2005): this scale objectively determine a patient's ability (or inability) to safely balance during a series of predetermined tasks. It is a 14 item list with each item consisting of a five-point ordinal scale ranging from 0 to 4, with 0 indicating the lowest level of function and 4 the highest level of function and takes approximately 20 minutes to complete.

- Participants who are not associated with the NYU MS Care Center will need the following completed by a study physician:
  - Neurological examination
  - Medical history
  - Medication history
  - Physical examination

Otherwise, this information will be provided by their physician before their baseline visit.

- **Administration of questionnaires self-administered**

  12-item MS Walking Scale (12-MSWS): Measuring the impact of MS on walking ability [Hobart et al., 2003]
  9-item Fatigue Severity Scale (9-item FSS): Measuring the physical aspect of fatigue [Krupp et al., 1988]
  21-item Modified form of the Fatigue Impact Scale (21-item MFIS): 9 items for physical aspects, 10 items for cognitive aspects and 2 items for psychosocial aspects [Fisk et al, 1994]
  Visual Analogue Scale for fatigue (VAS- $F_{0\text{-}10}$): Measuring the perceived general fatigue on a scale from 0 mm (no fatigue) to 10 mm (extreme fatigue) [Hewlett et al., 2007]
  Visual Analogue Scale for pain (VAS- $P_{0\text{-}10}$): Measuring the pain rating on a visual analogue scale from 0 mm (no pain) to 10 mm (severe, worst pain)
  54 items Multiple Sclerosis Quality of Life (54-MSQOL): multidimensional health-related quality of life measure that combines both generic and MS-specific items into a single instrument

5.3 Study Schedule

5.3.1 Screening

- Obtain informed verbal consent from potential participant to discuss study and medical history
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Schedule study enrolment visit for participants who are eligible and available for the duration of the study.

5.3.2 Enrollment/Baseline (Visit 1)

- Obtain informed consent of potential participant verified by signature on study informed consent form
- Verify inclusion/exclusion criteria (Section 5.1)
- Obtain demographic information, medical history, medication history
- Neurology Exam/Obtain EDSS (If participant is outside of NYU)
- Assessment of weight, height, and BMI
- Baseline measure: gait assessment with instrumented 10-meter walk (i-10MW), functional mobility assessment with instrumented Time Up and GO (i-TUG), Timed 25-Foot Walk (T25-FW), instrumented 2 minute walk (i-2MW) test, balance assessment with static posturography test, administration of Berg Balance Scale, and administration of questionnaires (9-item FSS, 21-item MFIS, MSWS-12, 54-MSQOL, and VAS- $F_{0\text{-}10}$)
- Cognitive assessment using BICAMS and CogState brief battery
- Provide instructions for wearing the ActiGraph device (optional)
- First tDCS session

5.3.3 Intermediate Remote Visits (Day 2 to Day 10)

- Administer the study treatment for 9 visits
  (Active stimulation: 20 mins of tDCS (2.5mA) while participants will complete physical training; Sham stimulation: 20 mins of tDCS sham stimulation, no current delivery during the session, while participants will complete physical training)
- Record adverse events as reported by participant with pain ratings (VAS- $P_{1\text{-}10}$) and self-reporting and rating possible adverse events during each stimulation session
- Monitoring of perceived exertion using Borg scale. Borg scale will be administered by study technician every 5 minutes during the 20 minutes PA training
- Instructions provided to participants after the session: no concurrent physical therapy for the entire duration of the study
- Optional: Only for the first (day 1) and follow-up (day 11) may participants' be asked to wear EEG electrodes. While performing cognitive tests (CogState and the SDMT) before and after the stimulation period, participant's EEG signals will be simultaneously recorded for ten minutes.

5.3.4 Treatment End visit (within 3 days after session 10)

- Gait assessment with instrumented 10-meter walk (i-10MW), functional mobility assessment with instrumented Time Up and GO (i-TUG), Timed 25-Foot Walk (T25-FW), instrumented 2 minute walk (i-2MW) test, balance assessment with static posturography test, administration of Berg Balance Scale, and administration of questionnaires (9-item FSS, 21-item MFIS, MSWS-12, 54-MSQOL, and VAS- $F_{0\text{-}10}$)
- Cognitive assessment using BICAMS and CogState brief battery

5.3.5 *Final Study Visit* (within 4 ± 1 weeks from the end of treatment i.e. Session 10)

- Gait assessment with instrumented 10-meter walk (i-10MW), functional mobility with instrumented Time Up and GO (i-TUG), and balance assessment with static posturography test, administration of Berg Balance Scale, Timed 25-Foot Walk (T25-FW)
- Administration of questionnaires (9-item FSS, 21-item MFIS, MSWS-12, 54-MSQOL, and VAS- $F_{0\text{-}10}$)
- Record participant's adherence to treatment program
- Cognitive assessment using BICAMS and CogState brief battery
- Collect the ActiGraph device (Optional)

5.3.6 Withdrawal/Early Termination Visit

Subjects may withdraw from the study at any time without prejudice to their care.

6 Assessment of Safety

A data safety monitoring plan (DSMP) will be implemented to ensure safety throughout the study. The study PI and Co-I Dr. Krupp will be responsible for the evaluation of safety.

There is a large body of literature indicating no known safety or tolerability risk for use of tDCS. Further, tDCS is currently being studied as an alternative to relatively higher risk treatments (such as medication) in special populations such as pregnant women and developmentally disabled children. Published studies in MS, including the work in our lab here at NYULH and Stony Brook Medicine, show tDCS to be a tolerable and safe treatment approach. Dr. Krupp and team at the MS Center are MS specialists with extensive experience in the assessment of patients with MS, including cognitive capacity, and including capacity to consent for numerous clinical drug trials where there is a substantially greater potential risk posed than what are the known risks for tDCS.

EEG is also established as a safe and painless procedure, with the major side-effect only being a temporary discomfort from the gel applied on the electrode patch to improve conductivity. It poses low risks even for critically ill populations as well such that is used as a continuous monitoring tool for patients during anesthesia

and in intensive care environments (Jameson, et al. 2006). Previous literature suggests that the combined use of EEG after tDCS does not increase any risks of harm. No complications or adverse events were reported for subjects whose EEG recordings were taken after performing motor tasks paired with tDCS stimulation (Polania, et al. 2012; Notturno, et al. 2013; Greecco, et al. 2014).

Actigraphy is also a safe tool that is increasingly utilized in clinical research. In a number of clinical trials, it has been used to monitor patient's responses to new treatments, and no safety concerns were raised when worn on vulnerable populations such as nursing home patients with advanced dementia, (Erdal, et al. 2018) and hospitalized elderly with high risk of delirium (Jaiswal, et al. 2018). Therefore, taken together, we do not believe that neither the simultaneous use of tDCS and EEG nor use of ActiGraph represents a situation where an independent party would be needed.

Weekly meetings between the PI, co-investigators, and study coordinators will review the clinical course and assessments of each subject. There are no pre-defined rules for stopping the study.

DSMP meetings will occur after the completion of every 10 study participants (all study procedures completed). Information to be reviewed at DSMP meetings will include adverse event rates and protocol compliance to ensure that the study is being conducted safely and is line with the current safety expectations associated with tDCS (i.e. no serious adverse effects are associated with tDCS).

Reports will be submitted at the annual review unless a change in the risk/benefit ratio has been identified from the safety and adverse event data (in which case a report will be promptly submitted to the IRB).

Non-Significant Risk Device Justification:

As described above, tDCS poses low risks to participants and our protocol is well-tolerated. To our knowledge, hundreds of tDCS studies in the US have all been designated Non-Significant-Risk (NSR) level (devices that are not: intended as an implant with potential for serious risk to health, safety, or welfare of subject; purported or represented to be for use in supporting or sustaining human life with a potential for serious risks; for use of substantial importance in diagnosing curing, mitigating, treating disease or otherwise preventing impairment of human health with potential for significant risk; otherwise presents significant risk to the health, safety, or welfare of a subject). For these reasons, the Soterix Mini CT, as used in this study, also qualifies as a NSR device.

While tDCS remains an investigational technique (simply because no company has applied to the FDA for approval to market tDCS for any given indication), tDCS is a broadly reproduced and tested techniques that is considered effective in modulating brain excitability in a manner that may support learning and with adverse events (different than sham) limited to tingling, itching, and redness that dispel after stimulation stops. In a prior study of use in a vulnerable population (developmentally disabled children), the FDA issued a NSR for tDCS device (see attached letter). The letter provided as an example of the FDA's designation of tDCS devices as abbreviated IDE. Because of its prior designation of tDCS devices as abbreviated IDE, trials do not typically seek further declaration. In the letter provided, Dr. Wasserman specifically sought FDA review of the trial due to the use of tDCS in a vulnerable population (developmentally disabled children).

To date, hundreds of trials have been designated as non-significant risk by IRB review which provides its abbreviated IDE status. Results of completed trials, including our own work in MS using this protocol, have supported the risk designation provided by IRBs. The Stony Brook Medicine IRB confirmed the NSR and abbreviated IDE status of tDCS for our study and others at the institution. We have learned that the NYU IRB has also confirmed tDCS devices (including those manufactured by Soterix) as abbreviated IDE for current ongoing studies at this institution. The safety of this technique has been addressed and tested by multiple researchers (e.g., Hummel, et al.117; Fregni, et. al.19, 118; Nitsche, et al. 13, 24, 119; Priori, et al.120) who have concluded that tDCS, as applied in a manner similar to our proposed protocol, induces only temporary mood, cognitive / motor effects, and no negative side effects. For example, researchers at the National Institute of Neurological Disorders and Stroke (NINDS), Iyer et al.19 conducted a safety study on tDCS, investigating 20-minute sessions of 1 mA and 2 mA current stimulation with healthy controls (n=103). No negative effects were identified. Nitsche and colleagues found no measurable structural changes in brain tissue due to tDCS

121. In a meta-analysis of over 200 tDCS studies conducted from 1998 to 2010, 56% of studies mentioned adverse events, which were generally minor.

The most commonly reported side effects included itching, tingling, headache, burning sensation and discomfort limited to the scalp site where the tDCS electrodes were applied. To date, there have been no reports of seizures induced by tDCS. Importantly this is the case in normal volunteers, but also in different populations of patients, including patients with disorders where there might be an increased risk of seizures (e.g. Alzheimer's disease, recent stroke, epilepsy). A study from NYU on the use of tDCS in patients with epilepsy122 encountered no increase in complications of tDCS in the patients as compared with controls. Specifically, there were no instances of seizures induced by tDCS.

Non-invasive EEG is also considered to be a tolerable and safe routine procedure. As of today, it is designated minimal risk by IRB Review (a procedure in which the probability and the magnitude of harm or discomfort caused are not greater than those encountered in daily life). The fBASfor use intended in this study also qualifies as a minimal risk device.

Cubii Pro Elliptical complies with FCC part 15 FCC Rules. This equipment is minimal risk because it is a non-invasive elliptical machine widely available for at-home workout composed of pedal bike cycle motion with adjustable resistance. Participants will be informed of all safety precautions:1) Use Cubii Pro only while sitting; 2) Use Cubii Pro indoors on a level surface; 3) Cubii Pro only by holding the handle; 4) For ensure maximum grip with the pedals, we recommended wearing soft sole shoes and straps.

ActiGraph also qualifies as a minimal risk by IRB because it is a non-invasive, physical sensor or watch that is only applied to the surface of the body. To date, there are numerous actigraphy testing devices that have been cleared for 510(k) process, and specifically, ActiGraph wGT3X-BT, the device that is used for this study, has already been approved as a Class II medical device by the FDA. More information are provided in the User Manual attached.

The static posturography test performed with force platform is not associated with any risks. The procedure of the posturography test is considered to be tolerable and safe procedure routine.

Participants in all groups may find the questionnaires time consuming and potentially bothersome. Neuropsychological testing and the physical activity sessions may, in some individuals, be stressful or anxiety producing.

There is a small risk of loss of confidentiality. Participants will be assigned a study ID and their name will not be used on any of the information collected. The results of these data collected may be used for publication but will not include the participants' names. Data will be stored in an IRB-compliant manner that is consistent with MCIT's policies.

6.1 Specification of Safety Parameters

6.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Concurrent illnesses or injuries acquired during the course of the study should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

6.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

6.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

6.2 Classification of an Adverse Event

6.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

6.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent

assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- ***Related*** *– The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.*
- ***Not Related*** *– There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.*

6.2.3 Expectedness

The study PI and Co-I Dr. Krupp will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

6.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, Co-I's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.
Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

6.4 Reporting Procedures – Notifying the IRB

6.4.1 Adverse Event Reporting

Adverse event rates will be calculated and reviewed at DSMP meetings. Adverse event rates will be reported to the IRB as described previously. Should adverse event rates exceed the normal rates observed in the literature, the study PI will place the study on hold and review the safety of the study.

6.4.2 Serious Adverse Event Reporting

Serious adverse events that are related to the study device or interventions will be reported to the IRB within 24 hours of occurrence.

6.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within five business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within five business days of the IR's receipt of the report of the problem from the investigator.

6.4.4 Reporting of Pregnancy

Participants that become pregnant during the course of the study will be discontinued from treatment and will be asked to complete a concluding participation end visit that includes no risk or involvement of treatment. Only assessment will occur at the participation end visit.

6.5 Study Halting Rules

There are no pre-defined rules for stopping the study. Individual participants may be removed from the study by the PI and/or Co-I.

6.6 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events by Co-I Dr. Krupp.

Safety and tolerance of study protocols will be assessed via safety reports after every ten participants that complete the study. Signed memos including the details of the reports will be submitted to the IRB in a timely fashion.

7 Statistical Considerations

7.1 Statistical Hypotheses

Research hypothesis
There is a significant difference between active and sham groups by comparing primary and secondary outcomes at baseline and end treatment time.
Null hypothesis
There will not be a significant difference between active and sham groups

7.2 Description of Statistical Methods

7.2.1 General Approach

Study design of the study is a double- blind randomized controlled trial.

The primary, secondary outcomes and demographic variables will be examined with summary statistics, including means, medians, standard deviations (SD), minimum, and maximum values for continuous variables, and frequencies and proportions for categorical variables.
The characteristics of the participants in the two groups will be compared at baseline using two- sample t-tests for continuous variables and the chi-square test for categorical variables.
The Shapiro-Wilk test will be performed, histograms will be constructed, and measures of central tendency and dispersion will be calculated to test the assumption that distribution is normal. If the normality check will fail, a transformation of the data will be done as corrective procedures.
The general approach of statistical analyses will be a repeated-measures analysis of variance (RM-ANOVA) with tDCS (2 levels: Active and Sham) as the between-independent variable and Time (3 levels: Day 1, Day 10, and after 4-weeks) as the within-independent variable.
In the inferential tests statistical significance will be set at 5% and all p-values is two-sided.

7.2.2 Analysis of the Primary Efficacy Endpoint(s)

Gait speed and Stride length

- Continuous variable (repeated measure)
- The Shapiro-Wilk test will be performed: histograms will be constructed, and measures of central tendency and dispersion will be calculated to test the assumption that distribution is normal
- If normality check will fail a transformation of the data will be done as corrective procedures (transformation will be made according to data distribution)
- Repeated-measures analysis of variance (RM-ANOVA) with tDCS (2 levels: Active and Sham) as the between-independent variable and Time (3 levels: Day 1, Day 10, and After 4-weeks) as the within-independent variable. In the inferential tests statistical significance will be set at 5% and all p-values is two-sided.

7.2.3 Analysis of the Secondary Endpoint(s)

Time Up and Go parameters (temporal parameters: phase duration of Sit-to-Stand, Stand-to-Sit, Mid and End turning; speed rotation; antero-posterior, lateral and vertical acceleration in Sit-to-Stand and Stand-to-Sit phases)

- Continuous variable (repeated measure)
- The Shapiro-Wilk test will be performed: histograms will be constructed, and measures of central tendency and dispersion will be calculated to test the assumption that distribution is normal
- If normality check will fail a transformation of the data will be done as corrective procedures (transformation will be made according to data distribution)
- Repeated-measures analysis of variance (RM-ANOVA) with tDCS (2 levels: Active and Sham) as the between-independent variable and Time (3 levels: Day 1, Day 10, and After 4-weeks) as the within-independent variable. In the inferential tests statistical significance will be set at 5% and all p-values is two-sided.

Static Posturography Parameters or Sway Parameters (velocity of the COP on the AP or ML axes, COP velocity, COP path and COP Area)

- Continuous variable (repeated measure)
- The Shapiro-Wilk test will be performed: histograms will be constructed, and measures of central tendency and dispersion will be calculated to test the assumption that distribution is normal

- If normality check will fail a transformation of the data will be done as corrective procedures (transformation will be made according to data distribution)
- Repeated-measures analysis of variance (RM-ANOVA) with tDCS (2 levels: Active and Sham) as the between-independent variable and Time (3 levels: Day 1, Day 10, and After 4-weeks) as the within-independent variable. In the inferential tests statistical significance will be set at 5% and all p-values is two-sided.

Questionnaire scores

- Continuous variable (repeated measure)
- The Shapiro-Wilk test will be performed: histograms will be constructed, and measures of central tendency and dispersion will be calculated to test the assumption that distribution is normal
- If normality check will fail a transformation of the data will be done as corrective procedures (transformation will be made according to data distribution)
- Repeated-measures analysis of variance (RM-ANOVA) with tDCS (2 levels: Active and Sham) as the between-independent variable and Time (3 levels: Day 1, Day 10, and After 4-weeks) as the within-independent variable. In the inferential tests statistical significance will be set at 5% and all p-values is two-sided.

7.2.4 Safety Analyses

Safety will be assessed through the number of adverse events that occur over the course of the study. Adverse event rates will be compared to that of published literature.

7.2.5 Baseline Descriptive Statistics

The demographic measurements and general characteristics (age, gender, height, BMI, EDSS scores) of the participants in the two groups will be compared at baseline using two-sample t-tests for continuous variables and the chi-square test for categorical variables. In the inferential tests statistical significance will be set at 5% and all p-values is two-sided.

7.2.6 Analysis of the Exploratory Endpoint (s)

The relationship between MRI measures previously collected at Standard of Care vists (total brain volume, white and gray matter volume, and degree of brain atrophy) and the participant's level of improvement (e.g. % change in gait and balance parameters such as walking speed and sway area) will be explored using Pearson's correlation.

7.3 Sample Size

The sample size is calculated on the primary endpoint gait velocity measured before tDCS treatments at baseline time in a population of individuals affected by MS (0.98 ± 0.23 m/s). According to previous study the variability of changes after tDCS combined with PA is on average around 20% in active group compared with baseline assessment.
To recognize as significant change in gait velocity (alpha level = 0.05), equal to 20% difference between baseline and end of the treatment, a sample size of 19 cases for each arm will provide a power of 80%.

7.4 Measures to Minimize Bias

7.4.1 Enrollment/Randomization/Masking Procedures

Blocked stratification will be used to randomize the participants to their respective study conditions. Block sizes of 4 and 6 will be used and the stratifying factor will be EDSS score (0-3.5 and 4.0-6.5).
For the purposes of masking, the two conditions will be indistinguishable by the participant and administering study technician as all that separates the two conditions will be the sham tDCS. Sham tDCS is very effective in making participants believe they are receiving true treatment. A separate study technician or study PI will prepare the participant's condition so as to ensure the double blind.

7.4.2 Evaluation of Success of Blinding

Participants will be asked at the end of the study what condition they believed they were assigned to: Active, sham, or that they cannot determine which.

7.4.3 Breaking the Study Blind

Study blind will be broken at the participation end visit.

8 Source Documents and Access to Source Data/Documents

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

9 Quality Assurance and Quality Control

Quality control procedures will be implemented beginning with data entry on NYULH's REDcap system. Any missing data or data anomalies will be communicated to the site(s) for clarification/ resolution to ensure quality of data.

10 Ethics/Protection of Human Subjects

10.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

10.2 Institutional Review Board

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

10.3 Informed Consent Process

All potential participants will complete a telephone pre-screening interview to ensure general eligibility. The study staff member speaking to the subject will provide the subject with an overview of the study and verbally receive their consent, under a waiver of documentation of consent, to complete the general eligibility screening. This phone screen is minimal risk to the participant and collected information will be maintained in secured,

locked files. A study referral log created in Microsoft Excel, in compliance with institutional policy, will be used to track participant eligibility prior to the process of informed consent and formal entry into the CRMS system. If a participant is not eligible, they will be considered a screen fail. No additional information will be collected. PHI will be destroyed immediately if a participant is not eligible or does not return to sign written consent/authorization to participate. Only study staff will have access to these records. Once the participant is generally eligible, the PI, or one of the trained study team members will review the consent form with the subject and explain the purpose of the study, the procedures, as well as risks and benefits. All questions will be addressed before acquiring the participant's signed consent. Dr. Lauren Krupp or one of the other IRB approved study physicians will be responsible for assessing the capacity to consent. We anticipate all eligible participants to have the capacity to consent and do not expect any participants to lose capacity to consent during the study. An independent assessor will not be utilized.

10.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

10.3.2 Consent Procedures and Documentation

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of an interpreter, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

Process to Document Consent in Writing: After review of the consent form and prior to the start of the first session, the PI or one of the coinvestigators will obtain written consent with a signature of the patient on the consent form. All original signed consent forms will be maintained in the study file, separate from the participant data.

Subject Capacity: All participants will be confirmed to have the capacity to provide consent by Dr. Lauren Krupp as described above. Further, those participants with estimated premorbid intellectual functioning and/or impaired reading ability (as determined by the WRAT-4 Reading Subtest) will be excluded.

Debriefing Procedures: No information will be purposely withheld from the subjects. A clinical neuropsychologist (PI) and the treatment team will be available to answer any questions concerning the tests and results, and provide initial feedback as warranted, including referral for clinical neuropsychological assessment.

Consent Forms: Participants will receive a NYU consent form to review and sign prior to participating in the study.

Documentation of Consent: The PI is responsible for ensuring that valid consent is obtained and documented for all subjects. An enrollment log will be maintained and consent forms will be kept in secure location separate from the participant's data.

10.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

All data collected will only be linked to the participants' identity through their subject ID. Physical data will be stored in locked containers at the study site (NYU) and digital data will be stored using REDCap. Only those approved by the IRB to be on the study will have access to data and linking key.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

11 Data Handling and Record Keeping

11.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. It is not allowed erase, overwrite, or use correction fluid or tape on the original.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

11.2 Study Records Retention

Study documents will be retained for 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

11.3 Protocol Deviations

Protocol deviations that are significant as judged by the Study PI will be reported to the IRB. Otherwise a note to file will indicate minor protocol deviations.

12 Study Finances

12.1 Costs to the Participant

There will be no cost to the participants.

12.2 Participant Reimbursements or Payments

Payment for Participation Participant will receive up to $100 in total compensation. They will be compensated $50 for the initial screening and baseline visit, and $50 for the final follow-up visit.

13 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.
Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

14 References

1. Angius, L., Mauger, A. R., Hopker, J., Pascual-Leone, A., Santarnecchi, E., & Marcora, S. M. (2017). Bilateral extracephalic transcranial direct current stimulation improves endurance performance in healthy individuals. Brain stimulation
2. Bastani, A., & Jaberzadeh, S. (2012). Does anodal transcranial direct current stimulation enhance excitability of the motor cortex and motor function in healthy individuals and subjects with stroke: a systematic review and meta-analysis. Clinical Neurophysiology, 123(4), 644-657
3. Bikson, M., Grossman, P., Thomas, C., Zannou, A. L., Jiang, J., Adnan, T., ... & Brunoni, A. R. (2016). Safety of transcranial direct current stimulation: evidence based update 2016. Brain stimulation, 9(5), 641-661
4. Bouchard, C. E., Shephard, R. J., & Stephens, T. E. (1994). Physical activity, fitness, and health: International proceedings and consensus statement. In International Consensus Symposium on Physical Activity, Fitness, and Health, 2nd, May, 1992, Toronto, ON, Canada. Human Kinetics Publishers
5. Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizzerio, B. G., & Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. International Journal of Neuropsychopharmacology, 14(8), 1133-1145
6. Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., ... & Ferrucci, R. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain stimulation, 5(3), 175-195
7. Cameron, M. H., & Wagner, J. M. (2011). Gait abnormalities in multiple sclerosis: pathogenesis, evaluation, and advances in treatment. Current neurology and neuroscience reports, 11(5), 507.
8. Chalah, M. A., Riachi, N., Ahdab, R., Créange, A., Lefaucheur, J. P., & Ayache, S. S. (2015). Fatigue in multiple sclerosis: neural correlates and the role of non-invasive brain stimulation. Frontiers in cellular neuroscience, 9
9. Chan, W., Dobbs, B., Shaw, M., Kasschau, M., Sherman, K., Krupp, L., & Charvet, L. (2017). Baseline affect predicts improved fatigue with telerehabilitation using remotely-supervised transcranial direct current stimulation (RS-tDCS) in adults with multiple sclerosis (MS)(P3. 343). Neurology, 88(16 Supplement), P3-343
10. Charvet, L. E., Dobbs, B., Shaw, M. T., Bikson, M., Datta, A., & Krupp, L. B. (2017). Remotely supervised transcranial direct current stimulation for the treatment of fatigue in multiple sclerosis: Results from a randomized, sham-controlled trial. Multiple Sclerosis Journal
11. Dalgas, U., & Stenager, E. (2014). Progressive resistance therapy is not the best way to rehabilitate deficits due to multiple sclerosis: No. Multiple Sclerosis Journal, 20(2), 141-142
12. DeBolt, L. S., & McCubbin, J. A. (2004). The effects of home-based resistance exercise on balance, power, and mobility in adults with multiple sclerosis. Archives of physical medicine and rehabilitation, 85(2), 290-297
13. Döring, A., Pfueller, C. F., Paul, F., & Dörr, J. (2012). Exercise in multiple sclerosis- an integral component of disease management. EPMA Journal, 3(1), 2
14. Elsner, B., Kugler, J., Pohl, M., & Mehrholz, J. (2016). Transcranial direct current stimulation (tDCS) for improving activities of daily living, and physical and cognitive functioning, in people after stroke. The Cochrane Library
15. Erdal, A., Flo, E., Aarsland, E., Selbaek, G., Ballard, C., Slettebo, DD., & Husebo, BS. (2018). Tolerability of buprenorphine transdermal system in nurinsg home patients with advanced dementia: a randomized, placebo-controlled trial (DEP. PAIN. DEM). Clin Interv Aging, 16(13), 935-946
16. Ferrucci, R., Vergari, M., Cogiamanian, F., Bocci, T., Ciocca, M., Tomasini, E., ... & Priori, A. (2014). Transcranial direct current stimulation (tDCS) for fatigue in multiple sclerosis. NeuroRehabilitation, 34(1), 121-127
17. Fleming, M. K., Pavlou, M., Newham, D. J., Sztriha, L., & Teo, J. T. (2017). Non-invasive brain stimulation for the lower limb after stroke: what do we know so far and what should we be doing next?. Disability and rehabilitation, 39(7), 714-720
18. Fregni, F., Boggio, P. S., Santos, M. C., Lima, M., Vieira, A. L., Rigonatti, S. P., ... & Pascual-Leone, A. (2006). Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease. Movement disorders, 21(10), 1693-1702

19. Halabchi, F., Alizadeh, Z., Sahraian, M. A., & Abolhasani, M. (2017). Exercise prescription for patients with multiple sclerosis; potential benefits and practical recommendations. *BMC neurology*, *17*(1), 185.
20. Hanken, K., Bosse, M., Möhrke, K., Eling, P., Kastrup, A., Antal, A., & Hildebrandt, H. (2016). Counteracting fatigue in multiple sclerosis with right parietal anodal transcranial direct current stimulation. Frontiers in neurology, 7
21. Haussleiter, I. S., Brüne, M., & Juckel, G. (2009). Psychopathology in multiple sclerosis: diagnosis, prevalence and treatment. Therapeutic advances in neurological disorders, 2(1), 13-29.
22. Iodice, R., Manganelli, F., & Dubbioso, R. (2017). The therapeutic use of non-invasive brain stimulation in multiple sclerosis–a review. Restorative neurology and neuroscience, 35(5), 497-509.
23. Jaiswal, S.J., McCarthy, T.J., Wineinger, N.E., Kang, D.Y., Song, J., Garcia, S., van Niekerk, C.J., Lu, C.Y., Loeks, M., & Owens, RL. (2018). Melatonin and sleep in preventing hospitalized delirium: A randomized clinical trial. Am J Med, S0002-9343(18), 30386-3.
24. Kaski, D., Dominguez, R. O., Allum, J. H., & Bronstein, A. M. (2013). Improving gait and balance in patients with leukoaraiosis using transcranial direct current stimulation and physical training: an exploratory study. Neurorehabilitation and neural repair, 27(9), 864-871
25. Kasschau, M., Sherman, K., Haider, L., Frontario, A., Shaw, M., Datta, A., … & Charvet, L. (2015). A protocol for the use of remotely-supervised transcranial direct current stimulation (tDCS) in multiple sclerosis (MS). Journal of visualized experiments: JoVE, (106)
26. Klooster, D. C., de Louw, A. J., Aldenkamp, A. P., Besseling, R. M. H., Mestrom, R. M. C., Carrette, S., ... & Carrette, E. (2016). Technical aspects of neurostimulation: focus on equipment, electric field modeling, and stimulation protocols. Neuroscience & Biobehavioral Reviews, 65, 113-141
27. LaRocca, N. G. (2011). Impact of walking impairment in multiple sclerosis. The Patient: Patient-Centered Outcomes Research, 4(3), 189-201
28. Meesen, R. L., Thijs, H., Leenus, D. J., & Cuypers, K. (2014). A single session of 1 mA anodal tDCS-supported motor training does not improve motor performance in patients with multiple sclerosis. Restorative neurology and neuroscience, 32(2), 293-300
29. Mori, F., Codecà, C., Kusayanagi, H., Monteleone, F., Buttari, F., Fiore, S., ... & Centonze, D. (2010). Effects of anodal transcranial direct current stimulation on chronic neuropathic pain in patients with multiple sclerosis. The journal of pain, 11(5), 436-442
30. Motl, R. W., McAuley, E., & Snook, E. M. (2005). Physical activity and multiple sclerosis: a meta-analysis. Multiple Sclerosis Journal, 11(4), 459-463
31. Motl, R. W. (2010). Physical activity and irreversible disability in multiple sclerosis. Exercise and sport sciences reviews, 38(4), 186-191
32. Nagano, H., James, L., Sparrow, W. A., & Begg, R. K. (2014). Effects of walking-induced fatigue on gait function and tripping risks in older adults. Journal of neuroengineering and rehabilitation, 11(1), 155
33. Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. The Journal of physiology, 527(3), 633-639
34. Nitsche, M., Doemkes, S., 2007. Shaping the effects of transcranial direct current stimulation of the human motor cortex. J. Neurophysiol. 97, 3109–3117
35. Nitsche, M.A., Cohen, L.G., Wassermann, E.M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P.S., Fregni, F., Pascual-Leone, A., 2008. Transcranial direct current stimulation: state of the art 2008. Brain Stimul. 1, 206–223
36. Palm, U., Segmiller, F. M., Epple, A. N., Freisleder, F. J., Koutsouleris, N., Schulte-Körne, G., & Padberg, F. (2016). Transcranial direct current stimulation in children and adolescents: a comprehensive review. Journal of Neural Transmission, 123(10), 1219-1234
37. Pau, M., Caggiari, S., Mura, A., Corona, F., Leban, B., Coghe, G., ... & Cocco, E. (2016). Clinical assessment of gait in individuals with multiple sclerosis using wearable inertial sensors: Comparison with patient-based measure. Multiple sclerosis and related disorders, 10, 187-191
38. Pau, M., Corona, F., Coghe, G., Marongiu, E., Loi, A., Crisafulli, A., ... & Cocco, E. (2017). Quantitative assessment of the effects of 6 months of adapted physical activity on gait in people with multiple sclerosis: a randomized controlled trial. Disability and rehabilitation, 1-11
39. Pau, M., Porta, M., Coghe, G., Corona, F., Pilloni, G., Lorefice, L., ... & Cocco, E. (2017). Are static and functional balance abilities related in individuals with Multiple Sclerosis?. Multiple Sclerosis and Related Disorders, 15, 1-6

40. Pearson, M., Dieberg, G., & Smart, N. (2015). Exercise as a therapy for improvement of walking ability in adults with multiple sclerosis: a meta-analysis. Archives of physical medicine and rehabilitation, 96(7), 1339-1348
41. Pedersen, B. K., & Saltin, B. (2015). Exercise as medicine–evidence for prescribing exercise as therapy in 26 different chronic diseases. Scandinavian journal of medicine & science in sports, 20(S3), 1-72
42. Peruzzi, A., Zarbo, I. R., Cereatti, A., Della Croce, U., & Mirelman, A. (2017). An innovative training program based on virtual reality and treadmill: effects on gait of persons with multiple sclerosis. Disability and rehabilitation, 39(15), 1557-1563
43. Pixa, N. H., Steinberg, F., & Doppelmayr, M. (2017). High-definition transcranial direct current stimulation to both primary motor cortices improves unimanual and bimanual dexterity. Neuroscience Letters, 643, 84-88
44. Saiote, C., Goldschmidt, T., Timäus, C., Steenwijk, M. D., Opitz, A., Antal, A., ... & Nitsche, M. A. (2014). Impact of transcranial direct current stimulation on fatigue in multiple sclerosis. Restorative neurology and neuroscience, 32(3), 423-436
45. Sánchez-Kuhn, A., Pérez-Fernández, C., Cánovas, R., Flores, P., & Sánchez-Santed, F. (2017). Transcranial direct current stimulation as a motor neurorehabilitation tool: an empirical review. Biomedical engineering online, 16(1), 76
46. Satow, T., Kawase, T., Kitamura, A., Kajitani, Y., Yamaguchi, T., Tanabe, N., & Mima, T. (2016). Combination of Transcranial Direct Current Stimulation and Neuromuscular Electrical Stimulation Improves Gait Ability in a Patient in Chronic Stage of Stroke. Case reports in neurology, 8(1), 39-46
47. Snook, E. M., & Motl, R. W. (2009). Effect of exercise training on walking mobility in multiple sclerosis: a meta-analysis. Neurorehabilitation and neural repair, 23(2), 108-116
48. Takemasa, S. (1998). Factors affecting QOL of the home-bound elderly disabled. The Kobe journal of medical sciences, 44(3), 99-114
49. Wagner, T., Valero-Cabre, A., Pascual-Leone, A., 2007. Noninvasive human brain stimulation. Annu. Rev. Biomed. Eng. 9, 527–565
50. White, L. J., & Dressendorfer, R. H. (2004). Exercise and multiple sclerosis. Sports medicine, 34(15), 1077-1100
51. White, L. J., & Castellano, V. (2008). Exercise and Brain Health—Implications for Multiple Sclerosis. Sports medicine, 38(2), 91-100
52. Woods, A. J., Antal, A., Bikson, M., Boggio, P. S., Brunoni, A. R., Celnik, P., ... & Knotkova, H. (2016). A technical guide to tDCS, and related non-invasive brain stimulation tools. Clinical Neurophysiology, 127(2), 1031-1048
53. Yotnuengnit, P., Bhidayasiri, R., Donkhan, R., Chaluaysrimuang, J., & Piravej, K. (2017). Effects of Transcranial Direct Current Stimulation Plus Physical Therapy on Gait in Patients With Parkinson Disease: A Randomized Controlled Trial. American journal of physical medicine & rehabilitation
54. Notturno, F., Marzetti, L., Pizzella, V., Uncini, A., & Zappasodi, F. (2014). Local and remote effects of transcranial direct current stimulation on the electrical activity of the motor cortical network. Human brain mapping, 35(5), 2220-2232.
55. Polanía, R., Paulus, W., & Nitsche, M. A. (2012). Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. Human brain mapping, 33(10), 2499-2508.
56. Grecco, L. A. C., Mendonça, M. E., Duarte, N. A., Zanon, N., Fregni, F., & Oliveira, C. S. (2014). Transcranial direct current stimulation combined with treadmill gait training in delayed neuro-psychomotor development. Journal of physical therapy science, 26(6), 945-950.
57. Jameson, L. C., & Sloan, T. B. (2006). Using EEG to monitor anesthesia drug effects during surgery. Journal of clinical monitoring and computing, 20(6), 445-472.
58. Gijbels, D., Eijnde, B. O., & Feys, P. (2011). Comparison of the 2-and 6-minute walk test in multiple sclerosis. Multiple Sclerosis Journal, 17(10), 1269-1272.
59. Motl, R. W., McAuley, E., Doerksen, S., Hu, L., & Morris, K. S. (2009). Preliminary evidence that self-efficacy predicts physical activity in multiple sclerosis. International Journal of Rehabilitation Research, 32(3), 260-263.
60. Pau, M., Coghe, G., Corona, F., Leban, B., Marrosu, M. G., & Cocco, E. (2015). Effectiveness and limitations of unsupervised home-based balance rehabilitation with Nintendo Wii in people with multiple sclerosis. BioMed research international, 2015.

61. Park, D. S., & Lee, G. (2014). Validity and reliability of balance assessment software using the Nintendo Wii balance board: usability and validation. Journal of neuroengineering and rehabilitation, 11(1), 99.
62. Pau, M., Porta, M., Coghe, G., Corona, F., Pilloni, G., Lorefice, L., ... & Cocco, E. (2017). Are static and functional balance abilities related in individuals with Multiple Sclerosis?. Multiple sclerosis and related disorders, 15, 1-6.Shaw MT, Best P, Frontario A, Charvet LE. Telerehabilitation benefits patients with multiple sclerosis in an urban setting [published online ahead of print, 2019 Jul 15]. J Telemed Telecare.2019;1357633X19861830.
63. Charvet LE, Shaw MT, Bikson M, Woods AJ, Knotkova H. Supervised transcranial direct current stimulation (tDCS) at home: A guide for clinical research and practice. Brain Stimul. 2020;13(3):686-693.
64. Benedict RHB, Amato MP, Boringa J, Brochet B, Foley F, Fredrikson S, et al. Brief International Cognitive Assessment for MS (BICAMS): international standards for validation. BMC Neurol. 2012 Jul 16;12:55.
65. Maruff P, Thomas E, Cysique L, Brew B, Collie A, Snyder P, et al. Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. Arch Clin Neuropsychol Off J Natl Acad Neuropsychol. 2009 Mar;24(2):165–78.
66. Berg K, Wood-Dauphinee S, Williams JI. The Balance Scale: reliability assessment with elderly residents and patients with an acute stroke. Scand J Rehabil Med. 1995 Mar;27(1):27–36.
67. Vsee: World's Largest Video Telemedicine Platform. 2015
68. TeamViewer: TeamViewer- the All-In-One Software for Remote Support and Online Meetings. 2015
69. Kasschau M, Reisner J, Sherman K, Bikson M, Datta A, Charvet LE: Transcranial Direct Current Stimulation Is Feasible for Remotely Supervised Home Delivery in Multiple Sclerosis. Neuromodulation Journal of the International Neuromodulation Society 2016

15 Attachments

Type	Objective	Measure	Time Frame	Safety Issue
Primary (Efficacy)	To determine the efficacy of the combination of the tDCS and PA to enhance gait ability	Change from baseline in walking abilities in instrumented 10 meter walking test (i-10MW)	1. Prior to treatment beginning 2. After treatment end 3. 4 weeks follow up	No
Primary (Feasibility)	To determine the feasibility of the protocol tDCS and PA	Number of participants who complete the treatment program	1. After treatment end	No
Secondary (Feasibility)	To determine the feasibility of remote supervised PA protocol paired with tDCS	Number of successfully completed sessions at-home	1. After treatment end	No
Secondary	To determine the efficacy of the combination of the tDCS and PA to enhance functional mobility	Change from baseline in functional mobility in instrumented Time Up and Go (i-TUG)	1. Prior to treatment beginning 2. After treatment end 3. 4 weeks follow up	No
Secondary	To determine the efficacy of the combination of the tDCS and PA to enhance static balance	Change from baseline in Sway Parameters	1. Prior to treatment beginning 2. After treatment end 3. 4 weeks follow up	No
Secondary	To determine the effect of the combination of the tDCS and PA on fatigue	Physical aspect of fatigue with 9-item FSS	1. Prior to treatment beginning 2. After treatment end 3. 4 weeks follow up	No
Secondary (Optional)	To determine the effect of tDCS on brain activity during the performance of cognitive test	Change in EEG signal before and after tDCS session	1. Prior to treatment beginning ad after treatment end during Day1 and Day 10 visit	No
Secondary	To determine the globally effect of the combination of the tDCS and PA	Physical, cognitive and psychosocial aspect with 21-item MFIS	1. Prior to treatment beginning 2. After treatment end 3. 4 weeks follow up	No
Secondary (Optional)	To determine the effect of tDCS treatment on level of daily physical activity and sleep	Intensity of physical activity, daily step count and number of sleeping hours	1. From baseline visit to follow-up visit	No
Secondary	To determine the effect of the combination of the tDCS and PA on walking ability	Subjective walking ability with MSWS-12	1. Prior to treatment beginning 2. After treatment end 3. 4 weeks follow up	No
Secondary	To determine the effect of the combination of the tDCS and PA on fatigue	Perceived general fatigue with VAS- F_{0-10}	1. Prior to treatment beginning	No

			2. After treatment end 3. 4 weeks follow up	
Secondary	To evaluate the presence of adverse events and subjective pain during stimulation	Experience of AE and pain ratings with VAS-P_{0-10}	1. After treatment end	Yes
Secondary	To determine the effect of the intervention tDCS+PA on processing speed	Change form baseline in processing speed (BICAMS, Cogstate Brief Battery)	4. Baseline 5. After treatment end 6. 4 weeks follow up	No

This section should contain all pertinent documents associated with the management of the study. The following lists a few examples of potential attachments:

- Investigator Agreement (for any investigator, other than sponsor-investigator, who participates in the study)
- Sample Consent Form
- Study Procedures Flowchart/Table
- Study Monitoring Plan

16 Schedule of Events

Activity	Screening	Baseline	tDCS +activity sessions	Study visit 11/ Treatment End Visit (approx. 3 days after end treatment)	Follow-up visit (Optional) [4 ±1 week post-Study Visit 10]
Study team procedures					
Consent	X				
Medical History	X				
Physical Exam	X				
Height		X			
Weight		X			
Neurological examination	X				
Randomization	X				
tDCS+ PA treatment		X	X	X	
Participant device compliance check				X	
Assessment of perceived exertion (Borg Scale)			X		
Instrumented evaluation of mobility					
i-10MW test		X		X	X
Timed 25-Foot Walk (T25-FW)		X		X	X
i-TUG test		X		X	X
Static Posturography Test	X	X		X	X
EEG assessment (Optional)		X		X	
i-2MW test		X		X	X
i-DPAS (Optional)		X	X	X	X
Questionnaires, Clinical Scale and Cognitive Assessment					
BICAMS		X		X	X
Cogstate Brief Battery		X		X	X
Berg Balance Scale		X		X	X
FSS		X	X	X	X
54-MSQOL		X			X
12-MSWS		X	X	X	X
21- MFIS		X	X	X	X
VAS- F $_{0\text{-}10}$		X	X	X	X
VAS- P $_{0\text{-}10}$		X	X	X	
Reported Adverse Events		X	X	X	