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Intra-Individual Variability in Cognitive Performance as a Marker of Prodromal Disability in MS

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NYULMC Study Number:	s21-01385
Funding Sponsor:	NYU Multiple Sclerosis Comprehensive Care Center
Study Product	• MRI: Siemens PRISMA 3T MRI scanner • tDCS: 1x1 tDCS Model 1300A Low-Intensity Stimulator (Soterix Medical, Inc) • Runscribe or G-Sensor wearable gait sensors
IND/IDE Number	
ClinicalTrials.gov Number	

Initial version (version 1): 12.14.2021
Amended (version 7.1): 3.15.2023

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), any other applicable US government research regulations, and institutional research policies and procedures. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

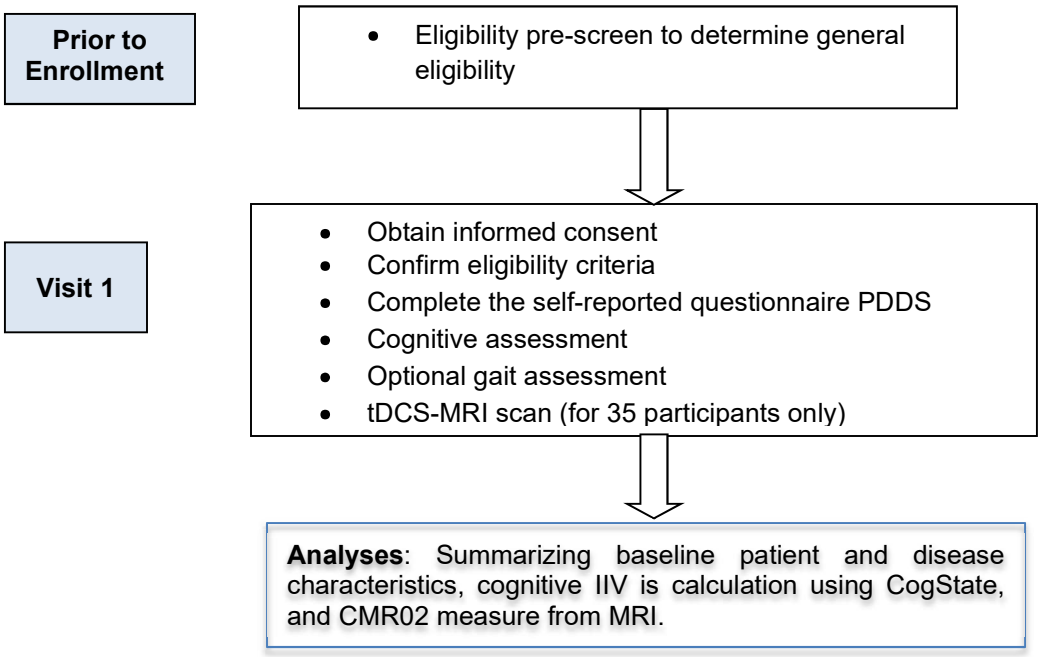
AE	Adverse Event/Adverse Experience
AHRQ	Agency for Healthcare Research Quality
BICAMS	Brief International Cognitive Assessment in MS
CBB	Cogstate Brief Battery
CBF	Cerebral Blood Flow
CBI	NYU Center for Biomedical Imaging
CFR	Code of Federal Regulations
CIS	Clinically isolated syndrome
$CMRO_2$	Cerebral Metabolic Rate of Oxygen
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DLPFC	Dorsolateral Prefrontal Cortex
PDDS	Patient Determined Disease Step
FFR	Federal Financial Report
fMRI	Functional MRI
FWA	Federalwide Assurance
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IIV	Intra-individual variability
IRB	Institutional Review Board
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSCCC	Multiple Sclerosis Comprehensive Care Center
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
pCASL	Pseudo-Continuous Arterial Spin Labeling
PHI	Protected Health Information
PI	Principal Investigator

QA	Quality Assurance
QC	Quality Control
RAVLT	Rey Auditory Verbal Learning Test
RIS	Radiologically isolated syndrome
RS-fMRI	Resting State-fMRI
RT	Reaction Time
SAE	Serious Adverse Event/Serious Adverse Experience
SDMT	Symbol Digit Modalities Test
SES	Socioeconomic Status
SOP	Standard Operating Procedure
tDCS	Transcranial Direct Current Stimulation
UAP	Unanticipated Problem
US	United States
ISD	Intraindividual Standardized Deviations

Protocol Summary

Title	Intra-Individual Variability (IIV) in Cognitive Performance as a Marker of Prodromal Disability in MS
Short Title	IIV Cognitive biomarkers in early MS
Funding Sponsor	National Multiple Sclerosis Society (NMSS)
Brief Summary	We recently received notice of award for the proposed study. The focus of this work is the evaluation of a measure of cognitive functioning- intra-individual variability (IIV) – derived from a computer-based continuous reaction time (RT) task (Cogstate) as an early marker of prodromal MS. This study is a prospective observational clinical study, where we will recruit adults with early MS (n=60) to complete a cognitive assessment and an optional gait assessment using Runscribe and G-sensor. Thirty-five [35] participants will also have a single 60-minute investigational MRI combined with 20 minutes of simultaneous tDCS. The MRI will repeat the protocol from our current study (ClinicalTrials.gov Identifier: NCT03564496, IRB i18-00548) using simultaneous transcranial direct current stimulation (tDCS) during the imaging acquisition.
Objectives	To evaluate cognitive IIV as marker of prodromal MS
Methodology	Observational study
Endpoint	- Primary outcomes: Cogstate Brief Battery (CBB) measures of reaction time/accuracy/IIV and Cerebral metabolic rate of oxygen ($CMRO_2$) - Secondary outcomes: Brief International Cognitive Assessment for MS (BICAMS) and IIV in gait measured with inertial wearable sensors (optional)
Study Duration	24 months
Participant Duration	Participation will include one that will last approximately 1.5-3.5 hours and will include a cognitive assessment, optional gait assessment. 35 participants will have a 60-minute MRI combined with simultaneous tDCS after the cognitive assessment. Participants may complete the MRI during a second visit.
Population	We will recruit 50 adults with early (prodromal) MS (e.g., clinically isolated syndrome (CIS),radiologically isolated syndrome (RIS), or subjects with a MS diagnosis of less than 5 years).
Study Sites	• 222 E 41st street, 10th Floor, NY, NY 10017 – NYU Dept. of Neurology • 240 East 38th Street, 13th Floor, NY, NY 10016 – NYU Multiple Sclerosis Comprehensive Care Center • NYU Langone Bernard and Irene Schwartz Center for Biomedical Imaging (CBI): 660 First Avenue, New York, NY 10016
Number of participants	N= 60
Statistical Analysis	Descriptive statistics, repeated measures ANOVA, simple correlations, and regression

Schematic of Study Design



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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

The goal of this project is to evaluate intra-individual variability (IIV) in cognitive performance, measured across response time (RT) on a computer task, as a marker of potential cognitive decline. We currently identify a patient's advancing neurological decline when it reaches the threshold for clinical detection of change. There remains an urgent need to identify patients before the onset of decline and disability[1]. Our scientific premise is that the initial neuronal dysfunction that defines prodromal neurodegeneration[2–5] can be reliably identified by subtle inconsistencies in cognitive processes[6–8]. We therefore propose using a clinically applicable approach to evaluate cognitive consistency as an indicator of prodromal neurological disability[1].

Cognitive consistency can be readily measured using simple computer-based psychomotor tasks[9–12], capturing intra-individual variability[13–15] (IIV) across an individual's repeated reaction times (RTs). IIV, compared to the conventional measures of accuracy or speed[16], is a highly sensitive marker of future health status at the population level[8,17] as well as in prodromal neurological disease[18–21].

For this project, we propose to develop the measurement of IIV towards its clinical application as prodromal marker in MS. We will utilize an innovative and accessible approach to measure IIV in patients that provides an age-normative score to represent cognitive consistency interpreted at the individual level. We will measure IIV measured with the simple and choice RT tasks in the computer-based Cogstate[9] platform. This brief (~7 min), practical, and widely available IIV measurement is clinically validated and with an extensive (n=95,162) normative data points for interpretation at the individual level. The cognitive IIV value will be compared to real time neuronal responses to tDCS as prodromal MS marker via a tDCS-MRI scan. This work will develop a clinical measure of IIV as behavioral measure of prodromal neurodegeneration that can guide early detection and, ultimately, prevention of disability.

2.2 Rationale

While we can detect cognitive impairment once it reaches the level of clinical impairment, there remains an urgent need for a measure that can identify patients *at risk* for impairment *before* the onset of disability. Our *scientific premise* is to measure risk in the prodromal/early stage- before disability occurs- by subtle inconsistencies in cognitive processes measured on simple computer-based reaction time tests. We will compare the IIV measure to neuroimaging markers of early disease. This work will advance us towards a clinical screening measure that can be used to detect the patients most at risk for near-term neurological disability in the context of MS.

3 Potential Risks & Benefits

3.1.1 Known Potential Risks

Risks associated with cognitive assessments and questionnaires: Completing questionnaires may produce some emotional distress in some participants. While we don't anticipate this will be a significant issue, participants will be allowed to take breaks as needed and may stop answering questions at any time without affecting their enrollment.

Risks associated with tDCS: There are no major risks associated with tDCS. Some people report head tingling, itchiness at the site of anodal stimulation, and a mild heating sensation. These irritations are usually mild and tolerable.

As in our previous MRI-tDCS study, we will use a Soterix Medical tDCS device (https://soterixmedical.com/research/1x1/tdcs) to administer ~20 minutes of stimulation during the MRI scan. The Soterix 1x1 tDCS device is outside of the MRI suite in the MRI control area. The cables used to connect the tDCS device to the tDCS headset/electrodes (which will be inside the MRI suite) are MRI-certified carbon cables. In addition, between the MRI control room and the MRI suite is a patch panel with an MRI filter. So far, no tDCS sessions delivered during the MRI scan were aborted due to safety or tolerability concerns. The most commonly reported side effects were skin tingling, sensations of warmth, and skin itching.

For the reasons referenced above, tDCS meets the criteria for an abbreviated IDE (non-significant risk medical device):

1. It is ***not*** intended as an implant and **does *not*** present a potential for serious risk to the health, safety, or welfare of a subject
2. It is ***not*** purported or represented to be for a use in supporting or sustaining human life and does ***not*** present a potential for serious risk to the health, safety, or welfare of a subject.
3. It is ***not*** for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and **does *not*** present a potential for serious risk to the health, safety, or welfare of a subject: the device will not be used for subject treatment and subjects standard medical treatment will continue regardless of their participation in the study
4. It ***does not*** otherwise present a potential for serious risk to the health, safety, or welfare of a subject[23-25].

Risks associated with MRI

Magnetic Field and Imaging Risks: MRI scanning involves the use of a magnet and radio frequency waves (much like an ordinary short-wave radio). There are no known risks or adverse effects resulting directly from exposure to magnetic fields and radio frequency signals used in this study, other than the potential risks associated with the scanning procedure summarized below. These potential risks are present with any MRI procedure.

Implanted Devices: Subjects, who have pacemakers, certain aneurysm clips, or shrapnel fragments or persons with metal in the eye, are at risk for injury from MRI examinations.

Collision Hazard: Because of the strong magnetic field associated with the scanner, one risk is that of a metallic object flying through the air toward the scanner and hitting you. To reduce this risk, all people involved with this study will remove all metal from their clothing and all metal objects from their pockets when in the scanning environment.

Hearing Protection: The MRI scanner produces tapping sounds during operation, which may reach very loud levels. To minimize any discomfort from this noise, the subject will be provided with disposable earplugs that suppress external noise levels but do not eliminate voice communication with the scanner operator. Alternatively, in some cases, they will have headphones instead of earplugs, which will deliver other sounds.

Claustrophobia (Fear of confined spaces): Some people feel claustrophobic (fear of small spaces) in the MRI scanner. If this happens, the scan will be stopped immediately and the subject will be removed from the scanner.

Quench Hazard (MR system failure): The MR scanner uses liquid nitrogen and liquid helium. It is remotely possible that the liquid nitrogen and helium will boil off rapidly and fill the magnet room with extremely cold dense gaseous nitrogen and helium, which can be dangerous if breathed for more than a few moments. The scanner operator will obviously detect this and immediately provide assistance to anyone inside the magnet room.

During the MRI, subjects will be in visual and verbal contact with the experimenter throughout the scan through a video monitoring system and can be removed quickly. In addition, participants are given a squeeze ball so they can signal the scanner operator in the event of an emergency. Some subjects have experienced dizziness or a metallic taste if they move their heads rapidly in the magnet. This, however, is only temporary and does not occur if the head is still. Acoustical noise is generated by the charging and discharging of the gradient coils which create the magnetic fields used to generate an image. Subjects will be wearing hearing protection that reduces acoustic noise by approximately 30dB. All possible measures will be taken to educate research personnel concerning the dangers of metallic projectiles in the magnet room and any individuals entering the magnet room will be thoroughly screened for ferromagnetic material.

Risks associated with optional gait assessments

Completing the optional gait assessment is associated with minimal risks. To minimize these potential risks, we will ask the participant to perform only tests that are familiar with (walking, standing from sitting position).

3.1.1.1 Other risks

There is minimal risk of breach of confidentiality. All data will be obtained on paper CRF and kept strictly confidential and stored in locked cabinets located at 222 East 41st Street, 10th Floor. Participants will be assigned a unique ID that will be used on all data collection instruments. The identifying link will be stored in a separate file and saved on password-protected NYU servers.

Unforeseeable Risks: While not expected, there may be risks associated with tDCS that are not known at this time.

3.1.2 Known Potential Benefits

There is no direct benefit to the participants expected from participating in this study. It is hoped that developing a method for early identification of cognitive decline in MS can help patients and clinicians develop clinical treatment plans in the future.

3.1.2.1 Incidental findings

Incidental findings on MRI scans are possible health abnormalities that are found during the course of subjects' participation in this study and are unrelated to the research topic but may be important for subjects and their physician to know about. Incidental findings that are identified by licensed radiologists may or may not have clinical significance as determined by the health professionals conducting this study will be communicated to Dr. Krupp, Sub-I for this study, who will also review the neuroimaging reports.

If clinically useful information is uncovered, Dr. Krupp will contact the subject on the telephone regarding the new information within 7 business days. Incidental findings reported to the subject will be recorded in the subject's medical record. A copy of the original image report will be provided upon patient request and participants will be encouraged to follow up with their treating physician outside of the study.

4 Objectives and Purpose

4.1 Primary Objective

The primary objectives are to characterize IIV and evaluate its underlying neuropathological mechanisms using neuroimaging techniques in prodromal/early MS. This work will develop a clinical measure of IIV as behavioral biomarker of prodromal MS that can guide early detection and, ultimately, prevention of disability.

4.2 Secondary Objectives

The secondary objective is to collect additional data to explore potential relationship among changes in IIV and cognitive function and in relation to gait variability.

5 Study Design and Endpoints

5.1 Description of Study Design

We will recruit 60 participants over a two-year period to assess the feasibility of developing the measurement of IIV towards its clinical application as prodromal marker of MS, and to test the association between IIV and the real-time neuronal responses to tDCS as prodromal MS marker via a tDCS-MRI scan.

Thirty-five (35) participants will complete 1 visit that will last approximately 3.5 hours. The visit will include consent, a cognitive assessment, an optional gait assessment, and a 1-hour MRI brain scan combined with 20 minutes of simultaneous tDCS. Participants may also complete the MRI on a separate visit.

Twenty-five (25) participants will complete 1 visit that will last approximately 1.5 hours (consent, cognitive assessment, and optional gait assessment). Procedures are exactly the same except that the tDCS-MRI will not be completed.

Group assignment will depend on eligibility, enrollment space (e.g. if one group reaches its target), and participant choice. The only difference between the two groups is that 1 group will have the MRI-tDCS procedure.

6 Study Enrollment and Withdrawal

6.1 Inclusion Criteria for All Participants

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

1. Ages 21-59 years old (inclusive)
2. Prodromal MS (defined by radiologically isolated syndrome ≤ 6 months from first MRI or clinically isolated syndrome ≤ 3 months from first clinical event)
3. MS diagnosis of ≤than 5 years

6.2 Exclusion Criteria (All Participants)

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

1. Below average estimated premorbid cognitive functioning (based on WRAT-4 reading recognition standard z-score < 85).
2. Presence of severe cognitive impairment (based on SDMT age normative z-score <-3.0).
3. Primary psychiatric disorder that would influence ability to participate.
4. Current uncontrolled seizure disorder.
5. Current substance abuse disorder.
6. History of head trauma in the past year (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).
7. Pregnant or breastfeeding

6.2.1 Additional Exclusion Criteria for tDCS-MRI Participants

1. Extreme claustrophobia
2. 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)
3. Treatment for a communicable skin disorder currently or over the past 12 months
4. Have any irremovable piercings, metallic based-tattoos, or MRI-contraindicated implants (e.g. pacemakers and defibrillators)

6.3 Vulnerable Subjects

N/A. Vulnerable subjects will not be recruited for this study.

6.4 Strategies for Recruitment and Retention

Research participants will be recruited from the NYU Langone Health MS Comprehensive Care Center (MSCCC) patient database. Additionally, an IRB approved study description will be posted on the website of the National Multiple Sclerosis Society and shared with the appropriate list-service. Moreover, IRB approved flyers will be posted in the clinic of the MS Comprehensive Care Center. Interested participants who learned of the study through word of mouth may reach out directly to the research team members. Patients who are seen by medical staff at NYU Langone Health, who fit eligibility criteria, will be referred by the study PI and sub-investigators. All recruiting division neurologists and medical staff 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, then a member of the research study staff will contact them. An IRB-approved phone script will be used to inform the patient about the study and to ask eligibility questions. Verbal responses will be recorded on a separate pre-screen verbal checklist.

If a potential subject is ineligible or does not provide written consent the information collected including all PHI collected for the purposes of this study will be destroyed immediately.

6.4.1 Use of Epic Information for Recruitment Purposes

N/A

6.5 Duration of Study Participation

Study participation involves 1 visit that will last approximately 1.5-3.5 hours. The study visit will include:

- Consent (~25 minutes),
- Eligibility clearance by study clinician (e.g. Neurologist or Nurse Practitioner), eligibility can be confirmed either over the phone, research video visit, or review of medical record from an external provider (30 minutes)
- Cognitive assessment (30 minutes)
- Optional gait assessment (20 minutes)
- ***[MRI-tDCS group only]*** tDCS tolerability test (2 min)
- ****[MRI-tDCS group only]*** MRI scan with simultaneous tDCS (60 minute scan plus an additional 40 minutes to walk to CBI, change clothes, complete MRI safety form, etc.).

  **Participants in the MRI-tDCS group may opt to complete the scan on a separate visit.*

6.6 Total Number of Participants and Sites

This study will recruit a total of 60 participants (target for participants who complete the tDCS-MRI is n=30 and target for participants who complete the cognitive assessment only is n=20 for total target of n=50, plus 10 to account for screen fails and withdrawals) at NYU Langone Health.

6.7 Participant *Withdrawal or Termination*

6.7.1 Reasons for Withdrawal or Termination

Participation in the study is voluntary and participants are free to withdraw from the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, 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.

6.7.2 Handling of Participant Withdrawals or Termination

If a participant wishes to withdraw from the study, they may do so at any point without adversely effecting any standard-of-care treatment. Participants will be provided with study team e-mail and contact number and can withdraw at any time.

Data of participants who withdraw or are terminated from the study may be kept for analysis if the data is usable (as determined PI).

6.7.3 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. 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:

- Determination of unexpected, significant, or unacceptable risk to participants.

- Demonstration of inefficacy that would warrant stopping
- Data that are not sufficiently complete and/or evaluable

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

7 Study Schedule

7.1 Eligibility Pre-screening

- Eligibility pre-screen to determine general eligibility.
- Obtain medical records.

7.2 Study Visit

- Obtain written informed consent (approximately 25 minutes or however much time is needed)
- Study clinician confirms patient'sdiagnostic eligibility based on inclusion/exclusion criteria in-person at the research visit. Alternatively, this can be done via phone, Zoom or Webex, prior to the baseline visit. Patients seen clinically at the NYU MSCCC may have their diagnostic eligibility confirmed without speaking to the study clinician prior to the baseline visit.
- Complete self-reported questionnaire-- Patient Determined Disease Steps[26] (PDDS, 5 minutes)
- Complete cognitive assessment (Cogstate and BICAMS, 30 minutes)
- Complete self-report questionnaire (paper form) (15 minutes).
- *(Optional for all participants)* Gait assessment (approximately 20 minutes)
- *[tDCS-MRI group only]* Perform tDCS tolerability test (2 minutes)
- *[tDCS-MRI group only]* Complete tDCS-MRI scan (40 minutes to prepare for scan, change, etc. and 60 minutes for scan [including 20-minutes of tDCS]).

8 Study Procedures

8.1 Baseline Procedures

After the participant provides written informed consent, the following research procedures will take place:

8.1.1 All Participants

- A study clinician will meet with the participant to confirm their eligibility according to the MS or prodromal MS inclusion criteria. Depending on patient and clinician availability, the clinician can either meet the patient in-person on the day of the research visit in a private room at NYU MSCC (222 East 41st Street, 10th floor, or 240 East 38th Street, 13th floor). Alternatively, the clinician can speak to the patient via phone, Zoom, or Webex prior to the baseline visit to confirm eligibility**.** Patients who are known to the NYU MSCCC can have their eligibility confirmed by a study clinician without meeting with the patient. Patients who have been diagnosed with MS less than five years and who receive their care from an external provider can provide their medical record or a letter from their neurologist indicating the date and nature of their MS diagnoses to confirm eligibility.

- Participants will complete a cognitive assessment (measures described in section 8.2).

- *Optional gait assessment*: Participants will have the option to complete a brief gait assessment administered by a trained study team member. Participants will be asked to walk at their self-selected speed back and forth for 2 minutes along a 30 meter hallway (222 East 41st Street, 10th floor, or 240 East 38th Street, 13th floor) in order to collect at least 30 steps to calculate the motor IIV. The gait assessment will be

repeated twice. During one walking task, participants will wear an inertial sensor around their waist (G-Sensor, BTS Bioengineering), while during the other will wear the inertial sensor on their shoe (Runscribe). The inertial sensor used will depend on availability. Both devices connect to a study iPad via Bluetooth and obtain data such as walking speed, balance, and stride length, etc. Identifying information will not be saved to the iPad or the sensors.

8.1.2 MRI-tDCS group only

- tDCS tolerability test: In a private room at CBI, a study team member will place the tDCS headset on the participant (dorsolateral prefrontal cortex montage, left anodal) and administer a 60-second tDCS stimulation test, with a 30-second ramp up to target 2.0mA, followed by a 30-second ramp down. Participants who cannot tolerate 2.0mA will be excluded from the study.

- MRI scan with simultaneous tDCS: At CBI, participants will be asked to complete an MRI Safety Questionnaire per standard protocol for radiology procedures. Participants who cannot confirm their pregnancy status will be given a urine pregnancy test and may only continue in the study if the test is negative. Participants will be asked to change into an MRI compatible patient robe in a private room and place their belongings in a locker for safe keeping.

  Next, they will be taken to the MRI suite and asked to lie down on the MRI table. A team member will place the MRI-compatible tDCS headset on the participant's head). Participants will be given a squeeze ball which can be used to alert the MRI technicians at any time during the scan should they need assistance. Participants will also be monitored by a study team member for the entirety of the MRI-tDCS scan. The set-up of the device and administration of stimulation will be done by an onsite study team member.

  The tDCS-MRI scan will last approximately one hour. The first 20 minutes of the MRI will not include tDCS stimulation. After 20 minutes, the tDCS device will ramp up to 2.0mA and deliver 2.0mA for 20 minutes. Then the tDCS will ramp down (30 seconds) and the final 20 minutes will be without stimulation. At the conclusion of the MRI, the participant will be paid for their participation.

8.2 Cognitive Assessments

- **Wide Range Achievement Test- 4th Edition (WRAT-4)** Reading Recognition Subset**:** The WRAT-4 is a brief test of single word reading recognition that provides a proxy of literacy and general intellectual ability.
- **Symbol Digit Modalities Test (SDMT)**: The SDMT is 90-second cognitive task in which the participant is shown a sheet containing rows of symbols. Each symbol corresponds to a specific number. The participant's task is to say out loud the number associated with each symbol. The SDMT is used as a general cognitive screen to detect severe cognitive impairment.
- **Brief International Cognitive Assessment for MS (BICAMS):** this battery tests mental processing speed and memory. BICAMS includes the following tests: Brief Visuospatial Memory Test (BVMT, requires the participant to look at a sheet with 6 shapes on it for 10 seconds and then draw as many shapes as they can from memory); the Rey Auditory Verbal Learning Test (RAVLT, requires the participant to recite back a list of words from memory as best they can), and SDMT described above.
- **Cogstate Brief Battery (CBB):** The core Cogstate RT tasks involve a deck of cards on a green background screen and the participant answers "yes" or "no" by hitting a keyboard key ("D" or "K") across repeated trials. Each task first includes instructions and practice period before the test begins

and takes approximately 3-4 minutes to complete (for a total of ~7 minutes). The representative timed RT scores are provided by the Detection task (indicating when a card is revealed; DET/simple RT), Identification task ("is the card revealed black or red?"; IDN/choice RT), and One-Back ("Is this the card that you just saw?"). Performance is characterized by near complete accuracy (i.e. all, or almost all, items are answered correctly), and validity checks are built into the scoring. The primary IIV outcome measure is calculated as intraindividual standardized deviations (ISD) in RTs across both tasks, measured in milliseconds and with log10 transformation.

8.3 MRI Sequences

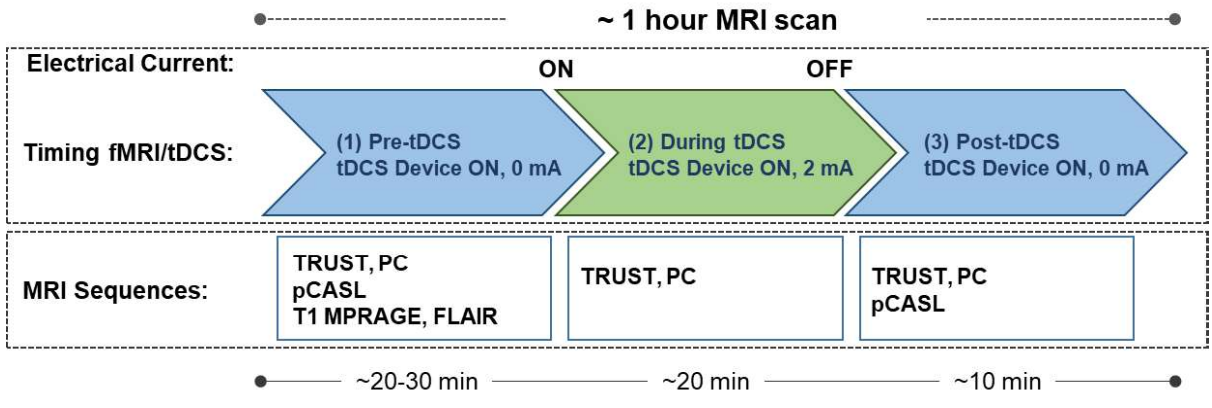
Cerebral metabolic rate of oxygen ($CMRO_2$) MRI: To quantify absolute $CMRO_2$, both TRUST MRI for quantification of venous oxygenation (Yv) and phase contrast (PC) MRI for quantification of total blows are needed. The imaging details were described in our previous paper[22]. The total scan time for $CMRO_2$ MRI is approximately 4 minutes.

Resting-state functional MRI (RS-fMRI): The sequence parameters for the RS-fMRI scans follow the ADNI protocol. We will use a 2D EPI sequence with SENSE partial-parallel imaging acceleration to obtain 3.3 × 3.3 mm (64 by 64 voxels) in plane resolution in forty-eight 3.3 mm transverse slices. An ascending slice order with TR/TE = 3000/30 ms, flip angle of 75°, and SENSE acceleration factor of 2 will be used. SPIR will be used for fat suppression. We will record 140 time points, for a scan time of 7 min.

Regional brain perfusion -Pseudo-Continuous Arterial Spin Labeling (pCASL): Increased neural activity is known to increase local cerebral blood flow through neurovascular coupling, which can also be monitored with Arterial Spin Labeling (ASL)[147] technique before and after tDCS. The CBF measured with pCASL in the current study will be used as an exploratory marker of regional integrity of neurovascular coupling (i.e., CBF and ∆CBF in the PFC substrate) and its association with clinical and neuropsychological outcomes.

MRI session includes 2 conditions: tDCS off (immediately before and after tDCS) and active tDCS (in red frame) (refer to Figure 3). The RS-fMRI is performed before the active tDCS (with device turned off) to assess the network connectivity changes without any current influence. The pCASL is performed before and after the active tDCS (with device turned off) to assess the integrity of the brain regional perfusion. $CMRO_2$ scans include PC MRI for CBF and TRUST MRI for Yv estimation; both sequences are not sensitive to the current-induced field inhomogeneity.

Figure 3. tDCS-MRI Timing, Protocol and Sequences



8.4 Laboratory Procedures/Evaluations

N/A

9 Safety and Adverse Events

9.1 Definitions

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).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries 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

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***.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

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. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

9.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to study participation should be recorded and reported immediately.

9.3 Reporting of Serious Adverse Events and Unanticipated Problems

For Narrative Reports of Safety Events
If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

9.3.1 Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events* that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:
The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g., analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using a Reportable New Information submission and will include a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution, and need for revision to consent form and/or other study documentation. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

9.4 Classification of an Adverse Event

9.4.1 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.

9.4.2 Relationship to Study Intervention

The study PI, in conjunction with CO-I and clinicians, will determine the relationship of any adverse events or unanticipated problems to study procedures and equipment.

9.4.3 Expectedness

The study PI 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 intervention.

9.5 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, or upon review by a study monitor. 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, clinician's assessment of severity, relationship to study intervention (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 participant completes study. Dr. Krupp will be informed of the occurrence of SAEs, review the SAE with the PI and study team, and assess the event based on institutional guidelines regarding relatedness to the study, harm to the patient, or if it is expected. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the PI as well as MD-Co Investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

9.6 Reporting Procedures – Notifying the IRB

9.6.1 Adverse Event Reporting

All adverse events will be reported to IRB per NYU policy.

9.6.2 Serious Adverse Event Reporting

All serious adverse events will be reported to IRB per NYU policy. Presence of an SAE will be included on data safety monitoring reports to the IRB and an immediate report (SAE that is related to study) will be submitted to the IRB within 48 hours of the event occurring. Dr. Krupp will review all SAE reports prior to their submission and follow up with each patient.

9.6.3 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 10 days of the investigator becoming aware of the event.

- 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 within10 days of the IR's receipt of the report of the problem from the investigator.

9.6.4 Reporting of Pregnancy

In the case of a positive pregnancy test, the participant will be informed of the test results and excluded from participating in the study.

10 Study Oversight

10.1 Safety Oversight

It is the responsibility of the Principal Investigator and Dr. Krupp to oversee the safety of the study. 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.

Data safety monitoring will occur at least on a tri-annual (3 times a year) basis and will include PI and Dr. Krupp review of safety and efficacy data including reports of tDCS side effects including skin irritation, itching, warming, and discomfort, potential distress from completing cognitive assessments and questionnaires, protocol adherence, regulatory documentation, enrollment (e.g. rate of enrollment, screen fails, withdrawals, etc.), unanticipated problems, and any issues that may arise during the course of research. Data safety monitoring reports will be submitted to the IRB on an annual basis at the time of continuing review. There are no predefined stopping rules.

10.2 Medical monitoring

Dr. Lauren Krupp, MD, Director of the NYU MSCCC, will serve as medical monitor for this study. Dr. Krupp will be responsible for assessing the severity and relatedness of SAEs. In addition, Dr. Krupp will be responsible for communicating incidental findings that have clinical significance found on the MRI scans to the patient.

10.3 Study Halting Rules

There are no predefined study halting rules.

10.4 Clinical Monitoring

Not Applicable

11 Statistical Considerations

11.1 Study Hypotheses

For the first aim with a cross-sectional representative cohort data, we hypothesized that higher IIV predicts a clinical classification of early cognitive impairment. For the second aim with longitudinal observational early MS cohort, we predict that higher IIV at baseline will predict greater decline. For the last aim with prospective recruitment of a prodromal cohort, we predict that that $CMRO_2$ response to tDCS to DLPFC will differentiate at-risk patients with high vs. low IIV.

11.2 Sample Size Determination

We aim to enroll 60 participants with prodromal MS to have n=50 evaluable participants (30 evaluable for the tDCS-MRI group and 20 evaluable for cognitive assessment group). As this is an exploratory protocol that is collecting data for future power analyses, the designation of recruiting 60 human subjects is arbitrary. Showing the feasibility of using Cogstate by this initial sample of participants, future studies can be conducted with properly powered samples to build a larger database. Recruitment of 60 participants would allow for enough data for assessing feasibility.

11.3 Statistical Methods

For the cognitive measures, the scores will be transformed to z scores to adjust for age: Each individual IIV value will be transformed into an age-normative z score using the Cogstate normative database (n=95,162). This will result in an age-adjusted IIV z score for use in all analyses described below.

BICAMS tests of SDMT, RAVLT and BVMT-R will be similarly converted to age-normative z scores using the most recently available databases[133–136]. A single BICAMS score will be computed as the average of z scores across the three measures[49].

Baseline patient and disease characteristics will be summarized for the 60 participants enrolled into this cohort. The primary focus in this cohort is to evaluate IIV along with changes in $CMRO_2$ during stimulation as described above as predictors of disease status. Distributions of IIV values and $CMRO_2$ at baseline and during stimulation, along with changes in $CMRO_2$ will be summarized descriptively and graphically with BICAMS classes. Bivariate scatterplots will display the baseline, during, and changes with IIV levels. Pairwise correlations will be estimated as measures of association between these variables (with transformations of values if required). Based on prior data, the mean change from baseline in $CMRO_2$ in 31 patients =7.91, sd=10.17 (mean % change =5.61%, sd=6.72). Here, we will predict IIV based on the $CMRO_2$ measurements at baseline and in response to tDCS. Other covariates will be incorporated into these exploratory models. For the binary BICAMS classes, again AUCs for the ROC curves from logistic models will be used to evaluate the roles of $CMRO_2$ changes and IIV.
Sample size. With 50 evaluable participants, we can detect an $R^2 \geq 0.141$ from a univariable regression model and of 0.225 with 5 independent variables. The collected data for this prodromal cohort will serve as the basis for future longitudinal follow-up of this cohort.

11.3.1 Agency for Healthcare Research and Quality (AHRQ) Indicator

An additional feature of our analyses is the inclusion of environmental adversity represented by socioeconomic status (SES). For all participants, using the zip code of their home residence, we will use the AHRQ indicator as a single linear value of SES and quality of healthcare access. This indicator will provide secondary and exploratory testing of the role of SES in IIV and clinical disability benchmarks.

12 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the study.

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 initialed 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.

13 Ethics/Protection of Human Subjects

13.1 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.

13.2 Institutional Review Board

The protocol, informed consent form(s), 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.

13.3 Informed Consent Process

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention. The following consent materials are submitted with this protocol: informed consent form.

13.3.1 Consent Procedures and Documentation

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. Participants will be asked to read the ICF in a private room at an approved study location (MSCCC or CBI). Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Alternatively, participants can be emailed a PDF version of the consent form via SendSafe and the phone number of a study team member to contact after they have reviewed the form. The study team member will then explain the consent to the subject, and ask if the subject has any questions. If the subject agrees to participate, they will electronically sign the informed consent document and email it back to the study team. Consent forms will be IRB-approved and the participant will be asked to read and review the document. A study team member 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 family 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 study. 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.

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 a translator, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

13.3.2 Posting of Clinical Trial Consent Form

N/A

13.4 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.

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.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor (NMSS). In addition, only raw data will be shared with the study sponsor and the study sponsor will not have access to the identifying link which is stored on secure, password-protected NYU Langone servers.

The study monitor or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. Only IRB-approved members of the NYU research team will have access to the linked data. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

13.4.1 Research Use of Stored Human Samples, Specimens, or Data

N/A

14 Data Handling and Record Keeping.

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the study 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. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Paper CRF will be provided for use as source documents and maintained for recording data for each participant enrolled in the study.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close out or 5 years after final reporting/publication. These documents should be retained for a longer period, however, if required by local regulations. 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.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the study protocol or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to use continuous vigilance to identify and report deviations as soon as practicably possible after identification of the protocol deviation. All deviations will be addressed in study source documents. Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

15 Study Finances

15.1 Funding Source

This study will be funded by the National Multiple Sclerosis Society.

15.2 Costs to the Participant

Participants will not be responsible for any costs associated with this study.

15.3 Participant Reimbursements or Payments

Participants will be compensated $50 for completing the cognitive assessment and optional gait assessments and an additional $75 for completing the MRI-tDCS.

16 Study Administration

16.1 Study Leadership

Dr. Leigh Charvet (study neuropsychologist) and Dr. Lauren Krupp (MS neurologist) will oversee the cognitive data collection and collaborate with the NYU Langone Health Neurology divisions for the recruitment. Dr. Charvet will be responsible for the scientific aspects of the cognitive and optional measurement data collection and analyses. Dr. Yulin Ge, MD, NYU radiologist, will oversee the radiology aspects of the study.

17 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 study 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 study. The study leadership in conjunction with the NYU IRB and CIMU has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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 Committee 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.

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