Study Protocol 11/22/2021 Last IRB approval on 09/19/19

NCT03870048	tDCS to Lower Neuropathic Pain and Fatigue in People With Multiple Sclerosis

Prospective participants, men and women with MS, will be recruited. To accomplish this study, 20 participants will need to complete 3 randomly-ordered blocks of protocols (sham, 2 mA, 4 mA), separated by at least one week. Each block involves 5 daily sessions at the INPL. The duration of each session will be approximately one hour and will be completed at the same time of day for each subject. We expect data collection to last 6 months. Each session will be a combination of questionnaires, leg strength assessment, and an isokinetic fatigue test.

Leg strength assessment: Isokinetic (concentric/concentric) flexion and extension of the knee at 60°/s will performed five times to determine the more-MS affected leg. When strength difference between the left and right legs is less than 10%, the more affected side will be based on the participant's self-report.

Isokinetic fatigue test: Participant's will perform 40 consecutive repetitions of isokinetic concentric/concentric flexion and extension of the knee on the more-affected leg at 120 degree/sec.

In the initial session (i.e., Block 1, Session 1) subjects will 1) be consented, 2) complete the Patient Determined Disease Steps (PDDS) questionnaire, 3) the Fatigue Severity Scale (FSS), 4) Neuropathic Pain Questionnaire (NPQ), 5) Visual analog scale (VAS), 6) perform a leg strength assessment, 7) perform an isokinetic fatigue test, and 8) undergo either sham tDCS, tDCS at 2 mA, or tDCS at 4 mA, depending on the randomized block.

tDCS treatment protocol: A tDCS device (Soterix) will deliver a small direct current through two sponge surface electrodes (5cm × 5cm, soaked with 15 mM NaCL). The positive electrode will be placed over the motor cortex representation of the more affected leg, and a second electrode will be placed on the forehead above the contralateral orbit. The three protocols blocks (sham, 2 mA, 4 mA) will be performed in randomized order.

tDCS Block: The participant will receive tDCS for 20 min at an intensity of 2 mA or 4 mA while seated comfortably and quietly in a room. The intensity will start at 0 mA and will be incrementally increased to 2mA or 4 mA over the initial 30 seconds. At the 19:30 minute time point, the current will gradually be reduced from 2 mA (or 4 mA) to 0 mA.

Sham block: Identical to the tDCS block, except the participants will only receive the initial 30 seconds of ramp-up, after which the current will be set to 0 for the remainder of the 20 minutes.

The remaining sessions of first block (i.e. Block 1, Sessions 2-5) will be as follows: In Sessions 2 and 4, the subjects get the tDCS or sham treatment, after which they will complete the fatigue and pain questionnaires (FSS and NPQ). Sessions 3 will be the same as Sessions 2 and 4, except that the isokinetic fatigue test will be performed at the beginning (i.e., before the tDCS or sham treatment). Session 5 will start with tDCS or sham treatment, then the isokinetic fatigue

test, and finally the fatigue and pain questionnaires.
Blocks 2 and 3 will be completed in the same manner as Block 1, except that the subjects will not redo the PDDS, VAS, and BDI in Session 1 and the treatment will shift to either tDCS at 2 mA, tDCS at 4 mA, or sham, depending on how the blocks were randomized. Block 2 will be randomly assigned based on uncompleted stimulation blocks.

Duration of Relief – If the participant indicates any reduction in pain following the previous day's tDCS session, they will be asked to estimate how long their pain was reduced following the session. Additionally, one week following the last testing session (i.e., Block 2, Session 5), participants will be contacted via telephone and asked the following questions:
1. Was tDCS effective at reducing your pain?
2. If so, how long did you notice a reduction in pain following your final tDCS session?
3. Have you reduced your use of pain relieving medications since your last tDCS session?

STATISTICAL ANALYSIS The generalized estimating equation (GEE) framework will be utilized to assess changes over time in fatigue and quality of life measures. An interaction term between time and treatment will allow us to test the within and between-treatment differences over all time points. Using histograms, variable distributions will be assessed to decide which link function to specify when modeling each outcome. To account for the inherent correlation that occurs in repeated measures data, we will cluster on subject ID. In addition to examining the unadjusted relationship between the time-treatment interaction and each outcome, we will consider the addition of control variables, which will reduce the likelihood of unaccounted confounders. The control variables being considered for inclusion in the adjusted models are age, sex, and time since discharge/discontinuation of home isolation. For each outcome, models will be fit for all possible combinations of control variables. The predictor set that yields the smallest Akaike information criterion (AIC) will be considered the optimal control variable set to adjust associations between the main predictor and the outcomes. Statistical significance will be assessed at the $\alpha = 0.05$ level. Analyses will be conducted using SAS 9.4.