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Transcranial Direct Current Stimulation to Lower Neuropathic Pain in People With Multiple Sclerosis

Purpose

The purpose of this study is to investigate the effects of different intensities of transcranial direct current stimulation (tDCS) on neuropathic pain and fatigue in people with MS. We will conduct three different tDCS conditions (sham, 2 mA, and 4 mA) on 5 consecutive days each. We will evaluate pain and fatigue with specific questionnaires and measure fatigability with an isokinetic device.
Our research question is whether tDCS can lessen neuropathic pain and increase fatigue resistance in people with MS and if a higher intensity stimulation (4 mA) provides additional pain and fatigue improvements. We hypothesize less neuropathic pain and increased fatigue resistance after either of the tDCS sessions and that the 4 mA condition will better improve pain and fatigue compared with the 2 mA condition.

Significance and Background

People with Multiple Sclerosis (PwMS) are at an over five-fold increased risk of receiving treatment for neuropathic pain. This pain type appears to be the primary factor behind the overall increased risk of pain treatment for PwMS. However, the management of neuropathic pain syndromes is currently a challenging task because only 40% to 60% of patients experience a favorable outcome from pharmacological treatments. Several studies have shown that most of the currently available treatments, including antidepressants, opioids, and topical anesthetics, have limited long-term effectiveness and are often associated with moderate or even severe adverse effects. It is generally agreed that improved therapies are needed for addressing symptoms of MS such as neuropathic pain. Furthermore, to fight the opioid epidemic in the US, safer treatments are urgently needed.

tDCS has significantly advanced in the past 15 years as a treatment tool and has been successfully used by the PI. It has a theoretical advantage when compared with traditional neuropathic pain treatments because it directly affects central neural targets, thus having a potentially stronger effect on central sensitization. On the other hand, its effects may take longer to appear (i.e., only after 5–10 sessions, subjects may notice pain decrease). Because of its relatively low cost, ease of use, and safety profile, tDCS may be a suitable alternative treatment of pain in various disorders.

Several preliminary studies have demonstrated initial efficacy of tDCS for pain control. Our own preliminary case study on one PwMS, who was resistant to pain medication, using the same tDCS protocol proposed here (2 mA condition), showed reduced pain ratings (VAS, NPSI) after the 5 consecutive days. Additionally, because pain and fatigue are strongly correlated, we will investigate the effects of tDCS on fatigability in PwMS at the same time. Furthermore, because there is a potential to increase the benefits of tDCS by increasing stimulation intensity, a comparison of different intensities (2 mA and 4 mA) will also be conducted.

Methods

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 be 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.

Inclusion Criteria: medically diagnosed with Multiple Sclerosis, 18-70 yrs. of age, moderate disability (Patient Determined Disease Steps (PDDS) core 2-6), self-reported differences in function between legs, able to walk for 6 min, and presenting with chronic, drug-resistant, neuropathic pain. Chronic neuropathic pain will be defined as a constant or intermittent sensory symptom with unpleasant feelings or pain, lasting more than 1 month and having a stereotyped neurological distribution and superficial localization. To differentiate neuropathic from spasticity-associated pain, patients need to score greater than 0 on the Neuropathic Pain Questionnaire (NPQ) to qualify for the study. A minimum score of 40 (0 = no pain, 100 = worst possible pain) on the visual analog scale (VAS) for pain perception at baseline will be required to be enrolled in the study. All analgesic medications will be discontinued at least 24 hours before entering the study and not be used until study participation is completed.

Exclusion Criteria: relapse within last 60 days, high risk for cardiovascular disease (ACSM risk classification), changes in disease modifying medications within last 45 days, concurrent neurological/neuromuscular disease, hospitalization within last 90 days, diagnosed depression, and inability to understand/sign informed consent.

Enrollment and Consent

Prospective participants, men and women with MS, will be recruited from the MS Clinic in the Dept. of Neurology at UIOWA (Dr. John Kamholz), through advertisements on UIOWA Campus, and through mass email. For those recruited at the clinic, Dr. Kamholz will discuss the study with potential participants and provide them with a copy of the informed consent and/or consent summary (if requested) and a copy of the recruitment flyer to contact the other study personnel. All other experimental procedures will be performed in the INPL (Director: Thorsten Rudroff, PhD, FACSM). Interested individuals from any recruitment source (i.e., clinic, flyers, website, email) will contact study personnel and perform an initial phone screening via a

questionnaire. Contact information for the prospective participant will be accessible only to the research staff according to HIPPA regulations. After completion of the phone questionnaire, INPL personnel will schedule the participant's first visit (10 total).

During the first visit, subjects will review the consent summary and consent form before signing the consent document. The PI or research staff will answer all questions asked by the potential subject and the subject will be informed of all potential risks before the signing the consent document. Subjects will in no way be coerced to sign the consent form and will be informed that it is their choice whether to volunteer for this study. Even after subjects sign the consent, they are free to withdraw from the study at any time and for any reason.

Risks for subjects

Physical well-being: Potential risk include muscle cramps/spasms during strength testing.

tDCS safety: tDCS is a non-invasive brain stimulation technique in which a very weak electrical current is applied to the scalp. tDCS has been conducted on humans and animals for many years and no evidence has emerged to suggest that it is harmful or has ever induced a serious side effect. However, the safety of tDCS is dependent on current strength, electrode size, and stimulation duration. Accordingly, these parameters have been investigated to establish safe and effective stimulation parameters for tDCS applications in research involving human subjects. However, recently experts in tDCS research have indicated that investigation of higher intensity tDCS is warranted (Nitsche et al. 2017) The only side effects that have been reported when proper guidelines are followed are temporary tingling, itching, headache, or skin redness under the electrodes in some subjects. For example, a 2008 review of the approximately 100 human tDCS studies up until that time on healthy adults and patients found that 64 of these studies reported no side effects, 24 studies reported a temporary itching or tingling under the electrodes in some subjects, and one study reported skin redness. Furthermore, these slight side effects were of equal occurrence in subjects that received placebo stimulation in 7 studies. In addition, only two subjects in these 100 studies reported a mild headache. Similar findings have recently been reported in research and review articles (Nitsche et al. 2008; Hummel et al. 2008).

Physiological studies have also assessed the safety of tDCS when applied within the aforementioned stimulation guidelines. For example, there was no neuronal damage as measured by serum neuron-specific enolase (Stagg & Nitsche, 2011) or MRI measures of edema using contrast enhanced and diffusion-weighted MRI measures following administration of tDCS (Nitsche et al. 2004). Furthermore, tDCS did not negatively alter measures of neuropsychological function and EEG activity (Iver et al. 2005). Accordingly, rat studies using tDCS models emulating tDCS applied to humans (Liebetanz et al. 2009) showed that the current density needed to induce tissue damage or lesions was about 1429 mA/cm^2, whereas the current densities used in human studies are between 0.04 and 0.08 mA/cm^2 and in this proposal are 0.029 mA/cm^2 and 0.11 mA/cm^2. Lastly, safety and tolerability results from two of our recent studies currently under review for publication provide evidence that 4 mA tDCS is safe and well-tolerated, with most sensations and sensation severities similar to sham and 2 mA tDCS. In conclusion, the tDCS stimulation parameters in this study are identical to the most common in the literature and have been proven to be exceptionally safe and well-tolerated.

The probability is very unlikely that harm may occur (see above). Based on the available literature a slight headache should be the worst possible negative effect and should be very rare. In this case, non-prescription medication should relieve the headache within 1-2 hours.

PwMS in general have a higher fall risk.

There are no emotional or psychological, financial, legal or social risks.

This was a case report: No statistical analysis.