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Protocol Title: Effects of bodily illusion and tDCS on SCI-related neuropathic pain

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1) Protocol Title

Effects of bodily illusion and tDCS on SCI-related neuropathic pain

2) Objectives

Specific Aim #1: We aim to determine to what extent neuropathic pain following spinal cord injury (SCI) is reduced after a non-pharmacological treatment involving bodily illusion (BI) and transcranial Direct Current Stimulation (tDCS).

Specific Aim #2: We aim to determine the relationship between Body Representation (BR) and neuropathic pain after SCI by investigating BR measures (e.g. body image task) before and after the exposure to BI and tDCS. Electrophysiological (EEG) measures before and after exposure to BI and tDCS will be also investigated.

The working hypothesis is that a manipulation of the BR through a long exposure of BI and tDCS will reduce neuropathic pain symptom severity and sensory abnormalities. Moreover, this research will provide insights into changes of BR and EEG measures after SCI so far neglected, given the measures of EEG and body image task taken before and after BI-tDCS.

3) Background

Following SCI persistent neuropathic pain is a common clinical condition that negatively influences quality of life (QoL) and independent living of SCI individuals by interfering with sleep, mood, physical and social activities *(Wollaars et al., 2007)*. Unfortunately, the neuropathic pains that occur after SCI are often inadequately relieved by available treatments, with pharmacological gold standard treatments reducing pain by 50% or more in only one person out of seven *(Cardenas et al., 2013)*. Thus, interdisciplinary, multimodal treatment approaches are particularly important to consider in this population. Indeed, our recent qualitative research shows that a priority of many SCI individuals who experience severe neuropathic pain is to have better access to non-pharmacological treatment options.

Research shows that non-pharmacological intervention that synergistically modulates neural activity with the purpose of inducing changes in body representation (BR) decreases neuropathic pain *(Moseley, 2007; Soler et al., 2010)*. In particular the combination of tDCS (a non-invasive brain stimulation able to modulate neural excitability, depending on the polarity of stimulation) and different types of bodily illusions (like, rubber hand illusions and walking illusion) to manipulate BR induce analgesic effects *(Soler et al., 2010)*.

Body representation is a multidimensional concept requiring the integration and organization of multiple sensory inputs, such as somatosensory,

proprioceptive and kinesthetic coming from skin, joints and muscles with visual information *(Carruthers, 2008; Deneve & Pouget, 2004; Longo et al., 2010)*. Under normal circumstances these information are integrated to provide a coherent sense of one's own body *(Longo et al., 2010)*. BR can be manipulated by using non-invasive approaches that manipulates the interaction between vision, touch and proprioception, such as the rubber hand illusion (RHI) *(Botvinick & Cohen, 1998; Tsakiris & Haggard, 2005)* and walking illusion (WI) *(Moseley, 2007; Soler et al., 2010)*. In the RHI a prosthetic hand brushed synchronously with a participant's own hand is perceived being part of the participant's own body. Similarly in the WI a participant on a wheelchair can see his/her upper body on a mirror, while the lower part of the body is a projection on the screen of legs in motion. Both illusions are able to manipulate BR through vision and proprioceptive manipulations and reduce neuropathic pain.

In addition the use of tDCS over specific brain areas (e,g,. motor cortex) in combination with bodily illusions has been used to treat neuropathic pain given the long lasting analgesic effect. Moreover, the modulations of embodiment processes for an artificial limb (e.g. RHI), such as the sense of body ownership, have been shown to be induced by tDCS over posterior parietal cortical (PPC) areas. There is therefore evidence that modulation of PPC can temporarily induce changes in body representation.

Finally, EEG research(Boord et al., 2008; Vuckovic et al., 2014) suggests that SCI-related neuropathic pain is associated with increased EEG power spectra in the theta range (4–7 Hz) and decreased power in alpha (8–13 Hz) and beta (13-20 Hz). These power spectra variations are attributed to altered inputs from the thalamus, a phenomenon known thalamocortical dysrhythmia. Brain rhythms can be modulated via non-invasive neuromodulatory interventions. For instance, tDCS induces neuronal membrane excitability that leads to changes in cortical activity. Anodal tDCS has been shown to modulate spontaneous oscillatory brain activity in the resting brain (e.g., an increase in alpha and beta power) after stimulation(Mangia et al., 2014). In addition tDCS over posterior parietal cortical areas has been shown to modulate aspects of multisensory body representation and increase cortical response to incoming visuo-spatial stimuli(Grasso et al., 2020; Spitoni et al., 2013) important for body representation.

In this protocol we aim to stimulate PPC by using tDCS or sham (inactive t-DCS) and at the participants will undergo to bodily illusion (BI) sessions.

4) Study Design

Purpose: The study is a pilot study investigating to what extent neuropathic pain is reduced after BI-tDCS stimulation in participants with SCI and neuropathic pain. (See also objectives above)

Number of Participants: In this pilot study 16 participants with SCI and neuropathic pain will be enrolled.

Number of study arms: two study arms

Study model: Experimental arm (half participants will undergo BI-tDCS) and Sham comparator arm (half participants will undergo BI- inactive tDCS).

Inclusion and Exclusion Criteria

Inclusion criteria

SCI and chronic pain (SCICP) group (N=16): Participants will be men or women, 18-75 years of age, with an incomplete cervical traumatic SCI. Participants must have experienced neuropathic pain for a minimum of six months. They must have neuropathic pain in the moderate to severe category, which will be defined as a score of at least 4 on a NRS (range of 0 to 10). Participants must be willing and able to sign informed consent.

Exclusion criteria

General: Candidates will be excluded if they have: (1) major psychiatric disease/disorder (self-reported); (2) a significant neurological trauma besides SCI (3) a recent (one-year) history of alcohol or drug abuse (self-reported); (4) any other medical conditions in which transcranial DCS is relatively contraindicated, such as pregnancy, epilepsy and/or seizures.

Arms and Interventions

Groups	Arms and Interventions	Intervention
Group 1 (8 SCI with Pain)	Experimental arm	BI-tDCS over 2-4 weeks
Group 2 (8 SCI with Pain)	Sham comparator arm	BI-inactive tDCS over 2-4 weeks

Procedures Involved

Participants will complete Pain/Sensory examination, EEG recording at rest and BR measures before BI and tDCS exposure (or BI and inactive tDCS: sham) (PRE-Session 1), then they will undergo 10 study sessions of BI and tDCS (or sham), 30 min, during a period of 2-4 weeks (from Monday to Friday) (Sessions 2-11). Finally, they will complete Pain/Sensory examination, EEG recording at rest and BR measures after BI and tDCS exposure (or sham) (POST- Session 12). See details below.

Session 1 - Baseline	Sessions 2-11	Session 12
Screening: Information on Injury; Age; Sex; BMI, Inclusion/Exclusion criteria listed above	BI-tDCS	-
BR measures: Computer task: mental rotation of body parts		BR measures
EEG recording at rest		EEG recording at rest
Sensory and Pain Assessment: QST; NPSI; ISCIPBDS; PGIC		Sensory and Pain Assessment
Other Questionnaires: PGWBI; BDI; CDS, Illusion measure		Other Questionnaires

PRE-Session (1). This session is done in a single visit of a duration of three hours, however, if necessary, we will divide the tests in 2 visits over 1 week, to meet participants' need**.**

BR measures: A computer task (mental rotation of body parts) will be performed **PRE** and **POST** BI-tDCS (or BI and inactive tDCS:sham). The mental rotation of body parts is assumed to activate somatosensory representations, such as the body schema. In this task participants will be instructed to perform a computer task: the mental rotation task of body parts. They will observe images of hands or feet (left and right) on a computer screen or objects (left or right oriented) in different angle orientation and they will have to judge the laterality of the image (left or right). Reaction times will be measured and defined as a difference from image onset and participant's vocal response, accuracy (correct responses) will be also evaluated.

EEG recording at rest: A 64-channel Biosemi EEG-system will be used to record cortical activity under two conditions of 5 min each: while subjects will rest with their eyes closed (EC), and while they will rest with their eyes open (EO) keeping the gaze on a fixation cross in the middle of a computer screen. These measures will be performed at baseline (**PRE**) and directly after treatment completion (BI-tDCS or BI-sham) (**POST**). Absolute spectral power will be calculated in the frequency range of 4–35 Hz, as we will focus our analysis on theta (4–7 Hz), alpha (8–13 Hz), low beta (13-20 Hz) and high beta (20-30 Hz).

Questionnaires: First they will be requested to report their height and weight to calculate body mass index (BMI). Participants will be also asked to complete 4 questionnaires: the Neuropathic Pain Symptom Inventory (NPSI), psychological general well-being index (PGWBI) questionnaire, the Beck Depression Inventory-II (BDI-II) and the Cambridge Depersonalization Scale. We will also perform a pain assessment using the Pain Basic Data Set where participants will describe their pains and provide the Patients' Global Impression of Change (PGIC):

1.The psychological general well-being index, The PGWBI is a validated Health

Related Quality of Life (HRQoL) measure, widely used in clinical trials and epidemiological research to provide a general evaluation of self-perceived psychological health and well-being. Participants are required to indicate the answer that best applies to them, choosing one of the 6 options (Grossi et al., 2006). It is composed of 22 items, rated on a 6-point scale (0 to 5). The scores for all items can be summarized into a summary score, which reaches a maximum of 110 points, representing the best achievable level of well-being.

2.Beck Depression Inventory, 2nd Edition (BDI): The BDI is a self-report multiple choice questionnaire designed to assess depressive symptoms (Steer et al., 2001). Participants are required to rate their symptoms over the past two weeks from 0-3 with increasing scores reflecting greater symptomatology. It is composed of 21 items. Each item is rated on a 4-point scale ranging from 0 to 3. Range of depression: 0–13 minimal, 14–19 mild, 20–28 moderate, and 29–63 severe.

3.The Cambridge Depersonalization Scale is a well-validated scale designed to assess disturbance of the apparent reality of one's physical states, as well as, altered perception of bodily experience. Participants are required to indicate the Frequency (from 0 to 4) and the Duration (from 1 to 6) of the bodily experiences that they may have in their life *(Sierra & Berrios, 2000)*. It is composed by 29 items. Each one of the 29 items is rated on two independent Likert scales, one for frequency and duration. A total score is calculated by adding all item scores. It has been established a score cut off of 70, >70 it is considered a depersonalization disorder.

4.Neuropathic Pain Symptom Inventory (NPSI): The NPSI (Bouhassira et al., 2005) assesses pain symptom severity associated *with neuropathic pain.* The NPSI is a 12 items questionnaire with a range of scores from 0 to 10 for all items, except for questions number 4 and 7 where the response is open. With a Total score maximum of 100 (summation of the 10 items except of item 4 and 7) indicating a clinically relevant dimension of neuropathic pain syndrome. The NPSI is also constituted of 5 subscales with a maximum total score of 10, indicating the specific dimensions of pain (burning, pressing, paroxysmal pain, evoked pain and paresthesia/dysesthesia). The NPSI includes severity ratings of *10 pain descriptors reflecting* spontaneous ongoing or paroxysmal pain, evoked pain (i.e. mechanical and thermal allodynia/hyperalgesia) and dysesthesia/ paresthesia. In addition, the NPSI includes two temporal items for duration of spontaneous ongoing pain and paroxysmal pain. The NPSI allows discrimination and quantification of five distinct and clinically relevant dimensions of neuropathic pain. The NPSI has been shown to be both valid and reliable in heterogeneous chronic pain populations.

5. International Spinal Cord Injury Pain Basic Data Set (ISCIPBDS*)* The ISCIPBDS is a brief instrument that contains questions about clinically relevant information concerning up to three separate pain problems during the last week including pain interference with sleep, activities, and mood, pain intensity, and pain classification (Widerström-Noga et al., 2014). Respondents are asked to rate the interference items on a 0 to 10 scale.

Patients' Global Impression of Change (PGIC): The PGIC scale was designed specifically to assess patients' perception of changes following treatment (i.e., "feeling better" or "feeling worse"). It is a 7-point verbal scale, with the options "very much improved" (3), "much improved" (2), "minimally improved" (0), "no change" (0), "minimally worsened" (-1) "much worsened" (-2), and "very much worsened" (-3). It has been demonstrated that the subjective "much improved" and "very much improved" ratings indicate moderately important and substantial improvement and the PGIC is widely used in neuropathic pain studies.

Sensory and Pain examination: All participants are required to have an AIS score. A trained examiner will conduct a standard neurological examination for SCI, including determination of the level of injury and classification on the American Spinal Injury Association (ASIA) Impairment Scale (AIS):

- *Quantitative sensory testing (QST) using Medoc machine (Medoc Ltd, Ramat Yishai, Israel and FDA approved)* The sensory assessment is intended to detect and quantify positive and negative sensory signs indicative of somatosensory (dys)function. A standardized QST protocol is commonly used in clinical and research settings to provide essential information regarding an individual's sensory status and has been used extensively in our research group *(Widerström-Noga et al., 2016)*. As part of the QST protocol, we will also assess mechanical and thermal allodynia. Ascending somatosensory information is transmitted mainly via the dorsal column-medial lemniscal (body) and the trigeminal lemniscus (face) for innocuous tactile and proprioceptive sensations, and via the spinothalamic tract (body) and the trigeminothalamic tract (face) for thermal and pain sensations.
  Somatosensory thresholds will be measured at two standard test sites in all subjects, the right cheek, near angle of nose and the thenar eminence, center. The right cheek will be chosen because this site is above the level of injury for all subjects.
- *Assessment of thermal allodynia:* An allodynic response is a painful response evoked by a stimulus that is not normally painful. We will use two thermorollers [Somedic, Sweden], one set at 40°C (corresponding to approximately 7 degrees above normal skin temperature), and the other at 25°C (approximately 8 degrees below normal skin temperature). Moving the rollers along the skin surface enables quick location of areas with abnormal temperature sensibility. If the subject perceives the thermal sensation as pain, it will be interpreted as thermal allodynia and the subject will be asked to rate the sensation on an NRS.
- *Assessment of dynamic and static mechanical allodynia:* Dynamic mechanical allodynia will be investigated similarly to the method described by *(Cruz-Almeida et al., 2012)*, who used a soft brush and lightly brushed the skin in the painful area. If pain is evoked in a test

site, the participant will be asked to rate the pain intensity by using an NRS. Static mechanical allodynia will be assessed using Semmes-Weinstein monofilaments. Evoked pain intensity will be rated on an NRS.

- *Pain assessments*:
Numerical Rating Scale (NRS): Numerical rating scales are widely accepted and used for the measurement of pain intensity. In this study, we will use this scale to assess the subjects' ratings of pain sensation on a scale of 0 (no pain) to 10 (most intense pain imaginable). For pain history, the International SCI Pain Basic Data Set (ISCIPBDS, version 2.0) will be used.

Session 2-11) BI-tDCS

Participants will undergo 10 study sessions of BI and tDCS, 30 min, during a period of 2-4 weeks (from Monday to Friday) (Sessions 2-11). We will allow for up to 3 missed sessions.

BI procedure: Two types of illusions will be used 15 min each, the rubber hand illusion (RHI) and the walking illusion (WI) to target upper and lower limbs. In the RHI a prosthetic hand will rest inside a box in front of the subject's midline at the same distance in front of the subject's chest as the subject's hand is. The entire box will be covered by a mirror, which prevents the subject from seeing their hand. The procedure requires that participants will only see the rubber hand while stimulated (tactile stimulation by using a paintbrush) and at the same time their hand will be also stimulated but hidden from their view. This will create a visual illusion as the fake hand will be perceived as one's own hand. For the WI participants will sit in their wheelchair and a screen will be placed in front of them, composed by a half mirror (top part) and half projector-screen (bottom part). Participants will be instructed to move their upper body and observe themselves in the mirror, while online a video of a walking person will be projected on the half bottom part of the screen. This will give the illusion of walking. After each illusion we will ask participants questions about the strength of the illusion. We will use the body ownership subscale (5 items) of the 27 items that compose the psychometric perspective of the embodiment after bodily illusion by Longo et al. in 2008 *(Longo et al., 2008)*. The 5 items of the questionnaire include questions about the feeling of body ownership of the rubber hand and virtual legs, the response options range from -3 (completely disagree) to +3 (completely agree).

tDCS: Direct current will be delivered from a battery-driven, constant current stimulator (TCT Research Version, Hong Kong) using saline-soaked surface sponge electrodes (35 cm2). The anode will be placed over P4 (EEG 10/20 system) to target the right Posterior Parietal Cortex (rPPC), and the cathode over the contralateral supraorbital area. This electrode position is chosen because rPPC has been shown to be involved in

multisensory integration, BR and localization of somatic stimuli *(Azañón et al., 2010; De Vignemont, 2007; Makin et al., 2008; Wertheim et al., 2020)*. However, consistent with other tDCS studies on pain *(Soler et al., 2010)*, where the site of stimulation is contralateral to the painful body-part, if participants have not bilateral pain and the painful site involves only the right side of the body, the anodal electrode will be placed on P3, the left Posterior Parietal cortex (lPPC), and be therefore contralateral to the painful body-part. A constant current of 2mA intensity will be applied for 30 min during the BI (15 min RHI plus 15 min WI). The duration of the stimulation has been chosen as used in previous works *(Mameli et al., 2014; Ouellet et al., 2015)*.

In the sham session (inactive tDCS) there will be no stimulation. The procedure will be the same as the active tDCS but the machine will be turned off after 30 seconds.

tDCS it is not a medical device and it is considered a non-significant-risk device, meaning that it is a technique without expectation of any Serious Adverse Effect *(Bikson et al., 2016; Fregni et al., 2015)*.

In the United States tDCS is not FDA approved. Some companies have an FDA (Food and Drug Administration) regulation status of "investigational" which limits the device to investigational use and not for medical treatment (*Fregni et al., 2015)*. In the European Union, Canada, Brazil, Australia, and Singapore, specific tDCS products have been approved for treatment of various neuropsychiatric disorders. *(Fregni et al., 2015)*.

Research centers worldwide are allowed to test tDCS in controlled clinical trials. A list of tDCS trials can be found here: *clinicaltrials.gov*

POST- Session (12)

BR measures: The measure a computer task (mental rotation of body parts) will be performed also **POST** BI-tDCS (or sham) (See same procedure of PRE-Session 1 above). This session is done in a single visit of a duration of three hours, however, if necessary, we will divide the tests in 2 visits over 1 week, to meet participants' need**.**

5) Data and Specimen Banking

NA

6) Study Endpoints

For each objective:

Specific Aim #1

Primary Endpoint
Although the total NPSI score is the tentative primary outcome measure in this pilot study, all NPSI subscales and other outcomes will be examined for change and may therefore potentially be considered a primary outcome in the final analyses.

Outcome Title: Change in neuropathic pain severity
Outcome Description: Assessed by the use of the Neuropathic Pain Symptom Inventory (NPSI). The NPSI is a 12 items questionnaire with a range of scores from 0 to 10 for all items, except for questions number 4 and 7 where the response is open. With a Total score maximum of 100 (summation of the 10 items except of item 4 and 7) indicating a clinically relevant dimension of neuropathic pain syndrome. The NPSI is also constituted of 5 subscales with a maximum total score of 10, indicating the specific dimensions of pain (burning, pressing, paroxysmal pain, evoked pain and paresthesia/dysesthesia).
Outcome Timeframe: From Visit 1 (before tDCS-BI) to Visit 12 after10 study sessions (after tDCS-BI)

Secondary Endpoints

Although the change in sensory thresholds is a tentative secondary primary outcome measure in this pilot study, all QST modalities and other outcomes will be examined for change.
Outcome Title: Change in sensory thresholds
Outcome Description: Assessed by the Quantitative Sensory Testing. Thresholds for vibration, cool (1- 2ºC above adaptation temperature) and warm (1- 2ºC below adaptation temperature) temperature, cold (threshold around 45ºC) and hot (about 10º C) pain. Expressed in 0-130 micron for vibration;
Outcome Timeframe: From Visit 1 (before tDCS-BI) to Visit 12 after10 study sessions (after tDCS-BI)

Specific Aim #2
Primary Endpoint

The change in RTs is a tentative primary outcome measure in this pilot study. Therefore other outcomes related to Aim 2 will be examined for change and may therefore potentially be considered a primary outcome in the final analyses

Outcome Title: Change in performance of body part processing
Outcome Description: Assessed by a customized computer task, where individual reaction times will be measured in response to mental rotation of body parts. There is no a standard result, it depends on the RTs of each individual, usually from 250 ms to up 5000 ms, fastest and slowest response respectively in this kind of study.
Outcome Timeframe: From Visit 1 (before tDCS-BI) to Visit 12 after10 study sessions (after tDCS-BI)

All other measures not listed in these Endpoints are exploratory and they will be examined for change and potentially be considered a primary outcome in the final analyses.

Secondary Endpoints

The change in EEG measures is a tentative outcome measure in this pilot study. Therefore, other outcomes related to Aim 2 will be examined for change and may therefore potentially be considered a primary outcome in the final analyses.

Outcome Title: Change EEG measures after BI-tDCS but not after BI-sham-tDCS
Outcome Description: Assessed by using a 64 channel EEG system. We will evaluate absolute spectral power in the frequency range of 4–35 Hz, as we will focus our analysis on theta (4–7 Hz), alpha (8–13 Hz), low beta (13-20 Hz) and high beta (20-30 Hz).

Outcome Timeframe: From Visit 1 (before tDCS-BI or before sham-BI) to Visit 12 after10 study sessions (after tDCS-BI or after sham tDCS-BI).

All other measures not listed in these Endpoints are exploratory and they will be examined for change and potentially be considered a primary outcome in the final analyses.

7) Data Management

The ongoing protection of data and participant privacy is a recognized responsibility all project staff having access to this information, the Principal Investigator in particular. The following procedures will be applied toward the monitoring, management, protection, and integrity of data:

1. The electronic data are stored in controlled-access workgroups on secure and backed up file servers under the control of the UM Department of Information Technology.

2. Access to these workgroups is restricted to project personnel authorized by the PI.

3. Each project member has a unique logon ID, knows only his or her password, and will have access to data specific to his/her job.

4. Electronically scanned copies of the obtained medical records necessary for the establishment of study entry criteria (e.g. SCI diagnosis, etc.) will be kept on secure and backed up file servers under the control of the UM Department of Information Technology. Hard copies will be returned to the participant or destroyed by secure means.

5. Software databases (MS Access and Excel, IBM SPSS) will not contain individually identifiable or other sensitive information. A Subject ID, that is NOT based on individually identifiable information will be assigned to each participant's data.

6. A document linking the Subject ID number to the participant's identity will be under the control of the PI and maintained separately from the raw data and scanned medical records. This link will be maintained as long as the research or applicable law requires and then destroyed by secure means.

7. Documents with names, social security numbers, or other sensitive information (e.g. informed consents, W-9 tax forms, and payment request forms) will be maintained separately from research data in locked cabinets within the controlled access offices of The Miami Project to Cure Paralysis. These documents will be maintained and securely destroyed per UM policy.

8. A UM laptop with UM IT installed encryption may be used by the PI for data analysis, however, no individually identifiable data will be located on this laptop.

9. Procedures for reporting theft or loss of sensitive data are in place and familiar to the study investigators and staff who have access to, use, or store data.

Data Analysis: Parametric or non –parametric statistic will be performed depending on data distribution.

Risks to Subjects:

Risks/discomforts associated with completion of questionnaires: Some questions may be emotionally distressful to some participants or make them uncomfortable. Participants will be instructed that they can skip any questions which they do not wish to answer.

Risks/discomforts associated with measurement of sensory function (QST): Pain thresholds will be measured for cold and hot temperatures. Each stimulus trial will start at a neutral temperature (32 ºC) and will be increased (for hot pain) until the participant indicates that the stimulus has just become painful. This will result in slight discomfort for the participant. As soon as the participant tells the experimenter that the stimulus is painful, the stimulus will immediately be terminated. Cut-off temperatures are in place (50 ºC for hot pain) so that no extreme temperatures will be presented. The cut-off value is well below temperatures at which any skin damage would result. The equipment used for sensory testing has been used in our laboratory for many years, without any adverse events. This equipment is also used in many other laboratories and has an excellent track record.

Risks/discomforts associated with BI: bodily illusions are commonly used research tools with no risk for participants.

Risks/discomforts associated with EEG measures: EEG records brain activity at no risk to participants. The EEG is used with the only purpose of recording, the electrodes are placed on the scalp attached to a custom cap with prepared holes. We use an EEG system with active electrodes (Biosemi Active Two 64 channels: https://www.biosemi.com/faq/skin_preparation.htm) and so high electrode impedance are tolerated, and the system can be used without the usual skin preparation (scrubbing) to lower impedance. This minimizes discomfort and eliminates risks of infection. In the case of electrodes placed around the face, it is possible that participants with very sensitive skin may experience redness, however this will be very minor and solve within minutes. We use a low impedance highly conductive saline gel (Signa gel by Parker), formulated to maximize contact between the body surface and the Active electrodes, bacteriostatic, non-irritating, and non-staining.

Risks/discomforts associated with tDCS: the current applied is very weak (2mA) and there are not observed serious adverse effects associated with tDCS. Minor side effects have included (restricted to the electrode location) mild temporary burning or tingling at the site of stimulation, headaches and tiredness *(Bikson et al., 2016)*, it is a safe procedure widely used (see *(Nitsche et al., 2003; Poreisz et al., 2007)* for more information and safety aspects of tDCS use). It should be noted that other side-effects like nausea and dizziness can happen and also that they have been illustrated to occur at nearly the same rate as sham stimulation (fake stimulation) *(Brunoni et al., 2011)*. These sensations are not painful and go away when stimulation stops. When electrodes are placed too close to the eye, participants may experience phosphenes that go away adjusting the position of electrodes. tDCS it is not a medical device and it is considered a non-significant-risk device, meaning that it is a technique without expectation of any Serious Adverse Effect *(Bikson et al., 2016; Fregni et al., 2015)*. We use standard procedures, which means: no more than 2mA of intensity, not more than 40 min per session, with standard electrodes (pads) that are typically square 5 × 5 cm or 5 × 7 cm *(Bikson et al., 2016)*. It has been extensively used in human research and chronic pain *(Pinto et al., 2018)*.
Please note that there is no scientific evidence that suggests lasting injury or irreversible side-effects from tDCS, all the minor sides effects are temporary.

We will explain participants the device and the possible minor side effects and we will let them familiarizing for short time by applying a very small amount of current before to reach 2mA.

Adverse Events and Serious Adverse Events associated with electrical stimulation:

temporary skin redness, itching, and tingling. Other suggested but rare side-effects of tDCS include headache, nausea, and dizziness. These sensations go away when stimulation stops.

tDCS it is not a medical device and it is considered a non-significant-risk device, meaning

that it is a technique without expectation of any Serious Adverse Effect.

Participants will report to study team if any of these side effects will be experienced, we will keep record of any reported side effect.

If the effects are experienced as uncomfortable to participants so that the stimulation will need to be stopped, we will not consider any data collected related to those participants. Participants have the right to not continue the study, in this case new participants will be enrolled for replacement.

8) Potential Benefits to Subjects

Participants may experience reduction in pain sensation, and will better understand their own pain and associated factors.

9) Vulnerable Populations

Vulnerable populations, i.e., children, individuals with moderate to severe cognitive impairment, prisoners of the penal system, and women who are pregnant will not be considered.

10) Setting

The study will take place at The Miami Project to Cure Paralysis, University of Miami.

11) Resources Available

Dr. Widerstrom-Noga is the principal investigator of the Clinical Pain Research Laboratory of The Miami Project to Cure Paralysis. Her educational background is in cross-disciplinary pain research (pain physiology and pain psychology) and in the clinical management of chronic pain. She have performed human pain research for more than 26 years and in the field of spinal cord injury (SCI) for over 22 years. Dr Widerstrom-Noga has published 65 peer reviewed journal articles and written nine book chapters on pain and pain assessment. Her present research involves both qualitative and quantitative pain methodologies including quantitative sensory testing and MR spectroscopic brain imaging. She has adapted outcome measures used to classify and assess pain in other chronic pain populations to people with SCI and been instrumental in developing, presenting, and promoting the International SCI Pain Data Sets and the NINDS CDEs for SCI and Pain. She serves as the Chair or as a member in both National and International efforts to standardize pain outcome

measures and pain classification, and clinical guidelines related to pain. Dr Widerstrom-Noga has extensive interdisciplinary clinical pain research experience in persons with neurotrauma, including the use of a wide spectrum of pain outcome measurements and pain phenotyping.

Dr. Vastano is a postdoc at the neurological surgery department at the University of Miami, Miller School of Medicine. She as an MSc degree in Cognitive and Experimental Psychology and her PhD is in cognitive sciences. Her research is focused on understanding brain mechanisms of sense of agency (motor control). Her expertise in experimental psychology and cognitive neuroscience makes her profile crucial for conducting this study. She has several publications on sense agency. In this study Dr. Vastano will conduct all measurements as described in the procedures section. In Dr. Eva Widerstrom-Noga's lab, Dr. Vastano has been trained in pain research.

12) Prior Approvals

No prior approvals will be necessary before commencing the study

13) Recruitment Methods

Individuals will be recruited via the Miami Project volunteer database (provided monthly by the Director of Education and Outreach at the Miami Project to Cure paralysis. The Miami Project research volunteer database is as database of over 4000 potential and/or current research participants who have expressed an interest in being considered for participation our research studies. These participants and their responses to an intake form are then screened for eligibility for our current research studies) and by word of mouth. In addition, participants will be solicited through the website of the Miami Project at the University of Miami (the Miami Project has a website and twitter page where they may post our protocols information and people can contact us:
https://www.themiamiproject.org/participant/research-participation/current-studies/).

Flyers about the study will be placed in the Miami area clinics, physical therapy, and rehabilitation centers serving patients with SCI and in University of Miami rehabilitation clinics. The research team will be located at the Miami Project to Cure Paralysis and available to speak with participants about the study prior enrolment, to provide all the information needed. Potential study participants will be asked to contact the study coordinator if they are interested in participating in the study and schedule an appointment.

Remuneration: Participants will receive a **$250**

$50 after Sensory and Pain examination (QST); $50 after the first week; $150 at the end of the 2 weeks and completed tests.

14) Local Number of Subjects

The current study is a single site study. We identified a total sample size of 20 SCI individuals with neuropathic pain. Additional aspects of sample size determination are the type and significance level of the test employed.

15) Confidentiality

All data obtained in this study will be used solely for research purposes. Sources of research material include:
(1) questionnaires and interviews with the participants regarding pain (paper data);
(2) reaction times and accuracy (electronic data), as described in the Procedure section.
Data will be therefore both paper and electronic.
Data will be coded for computer analysis, all participants' personal information will be kept separately by research findings (separation of identifiers and data) during storage, use, and transmission:

Personally Identifiable Information: For each participant, a folder will be created that contains confidential information. Extensive precautions are taken to insure the privacy of participants and the confidentiality of data. Specifically, participant identity is numerically coded on all pages within participant folders. All participant folders are kept in confidential lockers in our office at the Miami Project to Cure Paralysis .
The Personally Identifiable Information including *name*, *gender*, *ethnicity*, and *relevant medical (limited to know if they have pain and if they receive any treatment)* and *personal information* (such as *address*, *birth date, telephone number, email address and social security number*) is kept in a centralized, restricted access location.
Only personnel directly associated with the study have access to these files.

Data: For each participant, a folder will be created that contains all data. This folder serves as a permanent archive of original participant data. Research data will entered into the computerized database using only the participant ID number, and without any identifying information that would compromise the identity and confidentiality of the participants.

All electronic data will be secured and password protected in UM servers.
All paper data and PII will be kept separated and secured in lockers in our office where only the research team will have access.

Choose the statements below that are applicable to this research:

26(a). Will the research collect protected health information or personally identifiable information from the EMR or from subjects at UHealth and/or JHS?

☐ Yes (If checked go to 26(b))

☒ No (If checked, go to Section 27)

26(b). Check the box next to the correct statement below

☐ Research Subjects will sign a HIPAA Authorization before the research will collect this data.

☐ Research Subjects will not sign a HIPAA Authorization for this data collection and the research is requesting a waiver of HIPAA authorization from the IRB. *(If checked, complete Section 17 below)*

26(c). How will the research store the data? *(See Section 26(e) below)*

☐ On a University of Miami electronic device (e.g. encrypted, password-protected computer)

☐ On a cloud-based storage system that is approved by the University of Miami

☐ On the secured JHS SharePoint environment *(required for protected health information or identifiable information collected from JHS records without a waiver of authorization from an IRB.)*

☐ Other, specify: Click here to enter text.

26(d) Select one of the following:

☐ The Principal Investigator (and/or Study Team members) will record (e.g. write down, abstract) data acquired in a manner that does not include any indirect or direct identifiers (listed in the instructions for Section 26 of this protocol), and the recorded data will not be linked to the individual's' identity.

OR

☐ The Principal investigator (and/or Study Team members) will record (e.g. write down, abstract) the data collected in a manner that does not include any direct identifiers (see list in the instructions for Section 26 of this protocol) of any subject. Instead, the Principal Investigator and/or Study Team members shall will assign a code (that is not derived in whole or in part from any direct or indirect identifiers of the individual) to each study subject and link the code to the study subject's identity. The link to each subject's identity and/ or other identifiable information will be maintained on a document separate from the research data.

26(e) Additional requirement for Jackson Health System Data:

This section applies to data that will be collected from JHS under a waiver of HIPAA authorization (without a signed HIPAA Authorization from the participant).

X☐ Not-applicable, no data will be acquired from JHS under a waiver of authorization.

☐ JHS data, including Protected Health Information (PHI) and/or Personally Identifiable Information (PII), acquired from JHS for this research under a waiver of authorization shall only be stored on the secured JHS SharePoint environment made available by JHS. I and the Study Team members shall not copy or store the JHS sourced personally identifiable information (PII), including protected health information (PHI) data to any other system, including any systems maintained or provided by the University of Miami. I and the Study Team shall only copy or transfer JHS-sourced data that has been properly de-identified in accordance with all requirements contained in the HIPAA Rules by removing all of the identifiers listed in the instructions for Section 26 of this protocol.

16) Provisions to Protect the Privacy Interests of Subjects

See above 5) Data Management.

17) Consent Process

The consent process will be conducted by Roberta Vastano, Loriann Fleming, Linda Robayo Riofrio and/or the PI Dr. Eva Widerstrom-Noga. The consent process will take place at The Miami Project to Cure Paralysis, The Christine E. Lynn Rehabilitation Center . To ensure candidates have full knowledge of all study obligations and potential risks and benefits; all candidates will read the common consent document and then have an open, two-way discussion with consenting staff to establish 1) that candidates have a full understanding of what their participation will entail, and 2) allow the candidates an opportunity to ask questions or express concerns and have them fully addressed before proceeding with the study. Participants can freely decide to participate taking as much time as needed. The research team will follow up by contacting the participant again. This process will be present throughout the study and the participant will continue to have access to both research staff and the PI to resolve any concern that may arise. The study population will be English-speaker since the investigators are English-speakers.

18) Authorization for Use and Disclosure of Protected Health Information (HIPAA)

If the research team will access patient medical records or other identifiable health information for this research, you must obtain a waiver of the requirement for written authorization from the patients to access their medical records.

Type of Request:

☐ Waiver of Authorization for access to medical record for subject identification/recruitment.

☐ Waiver of Authorization for access to medical record to obtain data for the research.

Confirm that you will destroy the Protected Health Information (PHI) you and/or your Study Team acquire receive from JHS and/or UHealth at the earliest opportunity.

☐ ***I confirm***

Confirm that the Protected Health Inform (PHI) you acquire from JHS and/or UHealth will not be re-used or disclosed to any other person or entity, except as required by law or for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible.

☐ ***I confirm***

If you are collecting health information from JHS under a waiver of authorization, you must read the paragraph below and sign the signature block to indicate your agreement:

X☐ Not applicable. This research will not collect data from JHS record under a waiver of authorization

Notwithstanding the preceding "I confirm" statements above, I agree that neither I nor any member of the study team listed on the IRB submission for this Protocol shall ever re-use or re-disclose any of the information acquired from Jackson Health System in any format, whether **identifiable or de-identified,** to any individual or entity without first obtaining written permission from Jackson Health System, even if such re-use or re-disclosure is permissible by law (e.g., HIPAA).

_____

PI Signature Date

19) Process to Document Consent in Writing

We will document the informed consent process in writing. A member of the research team will explain the research study and let participants to read the consent form, remaining available for any question and clarification. Once participants will understand and sign and date the consent, they will take part of the study. A signed copy of the informed consent will be provided to participants as well.

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