Combined peripheral (BreEStim) and central electrical stimulation (tDCS) for neuropathic pain management

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University of Texas – Houston Medical School Protocol (CPHS HSC-MS-xxxx**)**

1. Protocol Title:

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2. Background:

Neuropathic pain is a chronic condition caused by a primary lesion or dysfunction of the nervous system. It is characterized by spontaneous, ongoing pain, described as burning, shooting, prickling or electrical, and/or pain in response to innocuous stimuli (allodynia) and exaggerated pain in response to noxious stimuli (hyperalgesia)(Bennett 2010). Neuropathic pain has increasingly been recognized as an important contributor to suffering, poor rehabilitation outcomes and reduced quality of life of the persons with SCI. Currently, there is no effective pharmacological treatment. Surprisingly, only 7% of responders reported pharmacological treatment is effective for neuropathic pain following SCI in a postal survey (Finnerup et al. 2001a). On the other hand, pharmacological interventions are often associated with side effects, such as addiction, withdrawal, and constipation, and sedation which may affect participation in rehabilitation and/or life activities, etc. Mechanisms of neuropathic pain are not well understood. Pain is multi-dimensional, including sensational and affective (i.e., unpleasantness) components. These components are processed in parallel, and inseparable to each other (Price 2000; Frot et al. 2008). For example, when superficial tactile stimulation is applied to the hand area where acupuncture points are located, activation is seen only in somatosensory cortices. However, when the acupuncture points are stimulated, and pain is experienced by the subjects, activation of additional cortical areas, such as anterior cingulate cortex (ACC) and insula, is observed(Hui et al. 2000). ***Therefore, it is important that sensational and affective components of neuropathic pain could theoretically be modulated separately for therapeutic purposes.***

Among various neurostimulation techniques (Kotze and Simpson 2008), including transcutaneous electrical nerve stimulation (TENS) (Norrbrink Budh and Lundeberg 2004), electroacupuncture (Ulett et al. 1998), spinal cord stimulation (Finnerup et al. 2001b), deep brain stimulation (Murphy and Reid 2001), transcranial direct current stimulation (tDCS) (Fregni et al. 2006; Boggio et al. 2008; Boggio et al. 2009) has emerged as a promising non-invasive brain stimulation technique for pain management. tDCS uses a small weak current applied through two oppositely charge electrodes on the scalp to induce neuroplastic changes that can alter pain perception in patients with chronic pain patients, such as SCI patients. Both electrodes are connected to a battery-powered device that induces a constant electrical current (usually, at 2mA) for approximately 15 to 20 minutes (Moreno-Duarte et al. 2014). The analgesic effect of tDCS depends on electrode placement, however. In a recent study(Boggio et al. 2008), **anodal tDCS targeting primary motor cortex (M1) increases pain as well as sensory perception thresholds,** while anodal tDCS of dorsal lateral prefrontal cortex (DLPFC) only increases pain threshold, without altering sensation thresholds. Anodal tDCS targeting M1 is believed to specifically modulate excitability of cortico-thalamic pathways, thus altering the sensational component of pain, while DLPFC stimulation arguably

operates at medial pain pathways through cortical-striatal-thalamic-cortical loop, as such attenuating the affective component of the pain (Plow et al. 2012). In a recent review in 2014 (Moreno-Duarte et al. 2014), there are eight clinical trials using various neurostimulation techniques for chronic pain management in SCI in the last 15 years. Among though studies, there were 3 tDCS, two TES (transcranial electrical stimulation), 2 rTMS (repetitive transcranial magnetic stimulation) and 1 TENS. Overall, the effect was heterogeneous. However, SCI patients were "responsive" to tDCS. Furthermore, the effect was better and longer-lasting when tDCS was combined with visual illusion in two studies (Soler et al. 2010; Kumru et al. 2013).

We recently proposed an innovative treatment – Breathing-controlled electrical stimulation (BreEStim) for neuropathic pain management (Li et al. 2012a; Li 2013a). This technique was developed from our discovery of systemic effect of human voluntary breathing on motor function and pain perception (Li and Laskin 2006; Li and Yasuda 2007; Ikeda et al. 2009; Li and Rymer 2011; Li et al. 2012a; Li et al. 2012b; Li 2013a), In the BreEStim treatment (see details in (Li 2013a)), human voluntary breathing signal is used to trigger an external electrical stimulator. A single-pulse electrical stimulation is then delivered to peripheral acupuncture points. After receiving the BreEStim treatment to the acupuncture points on the ipsilateral forearm daily for a week, a patient with constant shooting phantom pain secondary to an above-the-knee amputation reported no more shooting phantom pain, although he was still able to feel the shooting sensation occasionally in the phantom limb(Li et al. 2012a).

In the recent study (Li 2013b), an SCI patient (male, 40 years of age, T8 ASIA A SCI resulted from traumatic injury 4.5 years ago) received a 5-day electrical stimulation (EStim) treatment first, waited for 1 week for washout, and then received a 5-day BreEStim treatment. The duration of a single electrical stimulus was 0.1 ms. Surface electrodes were placed on the right forearm for acupoints (Neiguan and Weiguan). BreEStim had a greater pain reduction effect than EStim. Similar to the observation in the patient with traumatic above-the-knee amputation (Li et al. 2012a), BreEStim to acupoints on the forearm was not likely to modify the sources of noxious stimuli at the level of SCI (thoracic area) or at the residual limb (i.e., lower extremity). Rather, **BreEStim modified how patients react to the noxious stimuli at the central level, i.e., the affective response to the same stimuli**. Our case reports suggest that patients could tolerate the same noxious stimuli better after BreEStim. This is possibly realized by increasing pain threshold. In other words, BreEStim is likely to influence the affective component of pain.

Therefore, we hypothesize that combined tDCS and BreEStim treatment improves pain control by targeting different components of pain simultaneously as discussed above.

3. Purpose of the Study:

In summary, anodal tDCS targeting M1 will be selected since this approach influences sensational components of pain perception. BreEStim is shown to modulate the affective component of pain perception. Therefore, we expect that that combined BreEStim and tDCS treatment has addictive analgesic effects as compared to BreEStim or tDCS alone. We will test this treatment in healthy subjects and for neuropathic pain management in common patient populations, such as brain injury (BI), spinal cord injury (SCI), and amputation.

4. Description of Study:

This study has 4 experiments. The main idea is to test the effectiveness of the new intervention for neuropathic pain management for healthy subjects and one patient population (SCI, BI, or amputation) in each experiment. We request to recruit 20 subjects (5 subjects each group for healthy, SCI, BI and amputation). Overall, We plan to adopt recently published BreEStim (Li et al. 2013) and tDCS(Boggio et al. 2008) research protocols in this experiment. Briefly, this will be a single-center, randomized, cross-over trial to determine whether there is additive analgesic effect of a single session of combined and BreEStim and tDCS stimulation in healthy, and other patient subjects.

Subject recruitment

A total of 20 patients is planned to be enrolled as a pilot study for the following patient populations: healthy, BI, SCI and amputation. The estimated number of total patients will be calculated based on our pilot study with 5 subjects for each group. Patient subjects will be screened at the outpatient clinic of TIRR Memorial Hermann Hospital. Subjects will be recruited and enrolled in the project if they meet the inclusion and exclusion criteria (see subject population).

The interventions/Experimental procedures

The experiment consists of 3 sessions, including 1) BreEStim + Sham tDCS (i.e., BreEStim only), 2) BreEStim +active tDCS, and 3) tDCS only. Three sessions will be conducted on three different days with an interval of at least 24 hours. In each session, a conditioning tDCS (active or sham) will be performed first, then followed by BreEStim.

Anodal tDCS targeting M1 (Boggio et al. 2008) will be used. During each session, subjects will receive either active or sham stimulation to M1. A pair of surface sponge electrodes (35cm^2) will be soaked in saline and applied to the scalp. The anode electrode will be placed over C3 according to the 10-20 system for EEG electrode placement. The reference cathode electrode will be placed over the supraorbital area on the opposite side. For all active tDCS conditions, DC will be delivered by a specially developed, battery-driven, constant current stimulator (Soterix Medical, NY) with a maximum output of 10mA. A constant current of 2 mA will be applied for 15 min (the effect is usually expected to last 1-2 hours after tDCS) (Boggio et al. 2008). After the 15-min tDCS (active or sham), BreEStim will follow immediately.

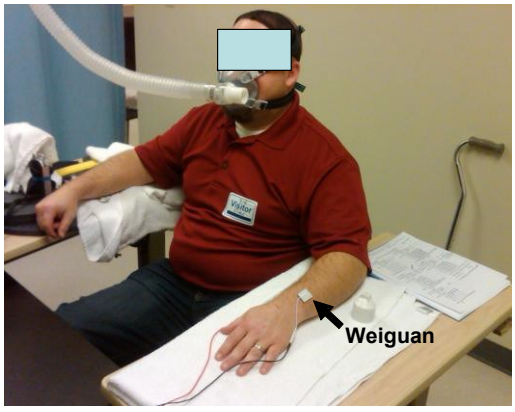

Figure 1 The experimental setup with BreEStim

The same BreEStim protocol (Li et al. 2013) will be used. Briefly, subjects will wear facemask that will be connected to a Pneumotach system to record breathing signals. Surface electrodes will be trimmed to be applied to acupuncture points (Neiguan and Weiguan) (see Figure for experimental settings). In the BreEStim treatment, a single-pulse (0.1 ms square wave) electrical stimulation is delivered to

acupuncture points when subjects are taking a fast, strong, and deep inhalation, similar to a deep breath but faster and stronger. It is important to mention that subjects control the intensity of electrical stimulation, to increase the intensity as tolerated gradually. Subjects will be explicitly instructed that aversiveness of painful stimulation is part of treatment protocol. To standardize, the total number of electrical stimuli is 200. Sufficient rest time will be allowed during the treatment. The BreEStim treatment takes about 30 minutes.

The above intervention will be applied to the following subject populations:

Experiment 1: the effect of combined BreEStim and tDCS treatment in healthy subjects

Experiment 2: the effect of combined BreEStim and tDCS treatment on neuropathic phantom pain in amputation subjects

Experiment 3: the effect of combined BreEStim and tDCS treatment on neuropathic pain in SCI subjects

Experiment 4: the effect of combined BreEStim and tDCS treatment on neuropathic pain in BI subjects

Specimens:
No specimens will be collected

5. Subject Population

In experiments 1-4, **5** subjects for each population (healthy, SCI, BI, and amputation) will be recruited and tested. An estimated number of patients will be obtained after the pilot study.

In experiment 1, healthy subjects will be recruited from residents, staff, therapists at TIRR Memorial Hermann in response to the flyer. The following inclusion/exclusion criteria will be followed (1) age between 18 and 60 years, (2) no clinically significant or unstable medical, neuropsychiatric, or chronic pain disorder, (3) no history of substance abuse or dependence, (4) no use of central nervous system-effective medication, (5) no history of brain surgery, tumor, pacemaker, or intracranial metal implantation or atrial fibrillation.

Patient subjects will be recruited from the TIRR outpatient clinic for experiments 2-4 for a total of 15 subjects.

Inclusion criteria: A patient who 1) has neuropathic pain after traumatic spinal cord injury or amputation or brain injury; 2) has chronic pain, >3 months; 3) is between 18 to 75 years of age; 4) is stable on oral pain medications at least two weeks. Patients are allowed to continue their pain medications, i.e., no change in pain medications.

Exclusion criteria: Patients will be excluded if they 1) are currently adjusting oral pain medications for their neuropathic pain; 2) have pain, but not neuropathic, e.g., from inflammation at the incision wound of the residual limb

or neuroma; 3) have a pacemaker in order to avoid possible side effects of electrical stimulation; 4) have amputation in their arm(s); 5) have SCI involving impairment of arms; 6) are not able to follow commands, or to give consent; 7) have asthma or other pulmonary disease; 8) are not medically stable; 9) have preexisting psychiatric disorders; 10) alcohol or drug abuse.

6. Data Analysis

Pre-intervention and post-intervention measurements include electrical sensation and pain thresholds and warm sensation and heat pain thresholds as used in our recent study (Li et al. 2013). In addition, visual analogue scores (VAS), modified visual analogue scores (mVAS) will be recorded in patient subjects. These measurements will be taken pre- and post-intervention for both sessions. VAS has been extensively used and validated (McCarthy et al. 2005). mVAS further quantifies the effect of pain reduction by measuring duration and amount of change in VAS, i.e., how much pain was reduced and how long it lasted (reduction × hours). It is necessary to note that pain rating is very subjective. This cross-over design uses subjects as their own control.

Heart rate variability as objective outcome measurements

We have been searching for non-invasive objective pain outcome assessment. Heart rate variability has recently recognized a physiological marker for pain assessment (Cowen et al. 2015), see also Appelhans & Leucken 2008 (both articles are uploaded to the iRIS).

We propose to add 5 minutes of Heart Rate recordings before and after the interventions. Experimental procedures and data analysis will be adopted from the above articles.

Two-way repeated measures ANOVA with factors INTERVENTIONS (3 levels, BreEStim only, tDCS only and tDCS+BreEStim) and TIME (pre- and post-intervention) will be used determined statistical significance for each threshold (electrical sensation and pain thresholds, and thermal sensation and pain threshold, mVAS). It is expected that BreEStim + tDCS will have better analgesic effect that BreEStim or tDCS alone.

7. Potential Risks/Discomforts:

The risks associated with this study are minimal. Electrical stimulation has been used extensively in clinical settings. Patients may feel uncomfortable, or even painful during electrical stimulation. The patients will be specifically instructed that they are encouraged to increase the intensity of electrical stimulation to the level they may feel uncomfortable, but they need to be able to tolerate at that level if given repetitively. They are also explicitly instructed to decrease the intensity of electrical stimulation if they cannot tolerate it. Surface electrodes can cause skin irritation from the tape adhesive or the electrode paste. Breathing through a face mask may be make patients feel uncomfortable. All tested subjects in the previous studies (approximately 70 subjects, including patients) tolerated the mask well.

All the tDCS safety papers (**poreisz 2007**- http://www.ncbi.nlm.nih.gov/pubmed/17452283, **kessler 2011**- http://www.ncbi.nlm.nih.gov/pubmed/22037128 , **nitsche 2003**- http://www.ncbi.nlm.nih.gov/pubmed/14580622) point to adverse effects as

itching/tingling. Over 600 studies have published using tDCS and Soterix units operate within the established current intensities/durations (0-2 mA, 10-40 min).

8. Benefits:

There are several potential benefits in this study: 1) direct benefit to subjects as their neuropathic pain may be relieved by the intervention; 2) benefit to the class of subjects: other patients in the same patient population may be benefit if the intervention is applied to them; 3) adding to the knowledge base: the findings will be definitely added to the knowledge base. Specifically, the study will provide evidence of an alternative and innovative intervention for neuropathic pain management.

9. Risk-benefit Ratio:

In view of the minimal risk, benefits and the knowledge to be gained far outweigh the risks.

10. Consent Procedures:

Informed consent will be obtained from the subject at the Motor Recovery Laboratory (B-107) at TIRR Memorial Hermann. After a subject is identified and interested in participating, informed, written consent will be obtained by the study coordinator.

11. Confidentiality Procedures:

In order to minimize risk to confidentiality, all data will be de-identified, coded with a study specific identification number, maintained on a password-protected server, and/or kept in a locked office. No findings will be released without written authorization by the subject.

12. Costs:

The subject will not be expected to pay any costs.

13. Payments:

Subjects will receive a Wal-mart gift card of $20 for each experimental session. The purpose of this payment is to improve subject recruitment and retention. Subject payment will be charged to PI's startup funds.

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