tDCS for Chronic Low Back Pain: A Study Examining the Effect of Transcranial Direct Current Stimulation on the Emotional Response to Chronic Low Back Pain

Principal Investigator:

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STUDY DESCRIPTION

The goal of this study is to investigate the role of central neural pathways in mediating chronic pain. The aim of the study is to test the effect of stimulating brain regions that are part of a network underlying central pain processing using a non-invasive brain stimulation technique, transcranial Direct Current Stimulation (tDCS). Prior studies have used tDCS to target both sensory related cortical areas (Fregni 2006) and those important for higher-order representations of pain (Mendonca 2011). This study will target brain regions important for the behavioral response to the chronic sensation of pain. The hypothesis is that stimulation of these brain regions can modulate not only the affective component of pain, but ultimately also improve functioning and quality of life. This hypothesis will be tested by treating study participants eighteen and older with chronic low back pain (CLBP) of greater than six months using tDCS. To be part of this study, participants must be Veterans that meet all the inclusion and exclusion criteria.

Specific Aims:

The aim of the proposed study is to determine effects of tDCS on the affective and behavioral component of chronic pain. The study will specifically target the dorsal anterior cingulate cortex (dACC), an important component of brain circuits that mediate learning in response to emotionally charged experiences. Measures of distress will be obtained due to the sensory component of pain to assess the degree to which pain interferes with the participants' daily activities and the emotional impact of CLBP on their lives.

Aim 1
To test the acute effects of active vs. sham cathodal (inhibitory) tDCS over dorsal anterior cingulate cortex (dACC), a region implicated in the affective components of pain in forty (40) patients in a controlled design.

Aim 2
To test the longer term effects of active vs. sham cathodal (inhibitory) tDCS over dACC in the same forty (40) patients in a controlled design.

Hypotheses:

Acute effects:

Hypothesis 1.1:

Distress associated with pain as measured by the West Haven-Yale Multidimensional Pain Inventory (WHYMPI) (affective subscale) and pain anxiety symptom scale (PASS-20) will decrease after ten (10) days of active, but not sham stimulation.

Hypothesis 1.2:

Pain-related avoidance and disability measured on WHYMPI (interference subscale), PASS20, and Rolland-Morris Disability Questionnaire (RMDQ) will decrease after ten (10) days of active, but not sham stimulation.

Hypothesis 1.3:

The perceptual component of pain, measured with the Defense & Veterans Pain Rating Scale (DVPRS) will not change.

Longer term effects:

Hypothesis 2.1:

Distress associated with pain as measured by the WHYMPI (affective subscale) and PASS20 will remain decreased at follow-up.

Hypothesis 2.2:

Pain-related avoidance and disability measured on WHYMPI (interference subscale), PASS20, and RMDQ will remain decreased at follow-up.

Hypothesis 2.3:

The perceptual component of pain, measured with the DVPRS, will not change.

BACKGROUND

Chronic pain is one of the single most challenging problems facing medicine. Costs associated with treating chronic pain and the resulting disability may exceed the combined cost of treating patients with coronary artery disease, cancer, and AIDS (Turk 2002). Of patients with chronic pain, the most prevalent syndrome is CLBP. Current treatments for CLBP consist mostly of opioid and non-steroidal anti-inflammatory medications that have been largely unsuccessful in curbing the growing societal cost of pain syndromes and providing long-term relief for patients. In the study proposed, the study investigators will test the efficacy of a novel approach to modulating brain areas important for processing the emotional dimension of pain.

Recent studies of chronic pain have suggested that the sensation of pain can give rise to maladaptive avoidance behavior and it is these behaviors that contribute to a significant part of pain-related disability. It has been posited that an adaptive mechanism exists for avoiding activities that result in further sensation of pain. In the short-term, this mechanism may protect a person from further injury. Continued avoidance of potential pain triggers, however, ultimately results in avoidance and discontinuation of daily activities that provide positive life experience, needed physical activity, and social support. This pattern of behavior ultimately leads to continued physical deconditioning, social isolation, and depressed mood (Crombez 2012), factors contributing to a higher risk of anxiety, depression, and suicide. In this study, we propose

stimulation of brain regions underlying the emotional component of pain, with the goal of interrupting the continuation and reinforcement of this cycle of maladaptive behavior.

Multiple interconnected brain regions are implicated in pain processing (Mackey 2004; Borsook 2010). These include areas of the brain directly responsible for processing sensory input such as the thalamus, primary and secondary somatosensory cortices, and regions important for mediating cognitive aspects of pain processing, such as dorsolateral prefrontal cortex (DLPFC), dorsal anterior cingulate cortex (dACC), medial and ventromedial prefrontal (mPFC and vmPFC, respectively), orbitofrontal (OFC), and insular cortex. The investigators will target those brain regions that play a role in emotional salience of pain processing. Specifically, our initial efforts will inhibit the activation of dACC. We posit that reducing the activity in dACC will decrease the emotional saliency of pain, impacting the degree to which CLBP causes disability.

The role of anterior cingulate cortex (ACC) in mediating pain processing is well supported. First, a mainstay treatment for chronic pain includes opioid medications. Though these medications act in multiple brain regions, ACC exhibits one of the highest densities of opioid receptors in the brain and is a primary site of action for these treatments (Vogt 1995). Second, selective surgical lesion of the cingulate cortex has been used to treat chronic pain since the 1960s. Importantly, following surgery, though patients reported still experiencing the pain, they were less bothered by it (Eisenberger 2004; Folzt 1968). This response supports the role of ACC in the affective component of pain processing. It is the goal of this study to determine whether a similar dissociation between the sensation of pain and the distress related to pain can be elicited by stimulating dACC using a non-invasive method, tDCS.

Transcranial direct current stimulation, or tDCS, is classified by the FDA as a minimal risk technique. tDCS applies low amplitude direct current to the scalp to modulate the excitability of underlying cortex. Several studies have shown promising results treating acute pain, neuropathic pain resulting from spinal cord injury, and chronic pain from fibromyalgia (Antal 2008; Lefaucher 2008; Fregni 2006). As in these studies, tDCS will be used to target areas of the brain that participate in pain processing at higher levels beyond simply relaying sensory information. By changing activity in the "affective tier" of brain networks implicated in responses to pain, the investigators expect to modify emotional responses and behaviors that add to its burden.

STUDY POPULATION

To be eligible for participation in this study participants must be eighteen years or older with a diagnosis of CLBP chronic low back pain and meet the inclusion and exclusion criteria (see below). There are no exclusions based on race, ethnicity or gender. The plan is to consent up to fifty (50) volunteers with a goal of enrolling forty (40) participants, twenty (20) in the treatment group and twenty (20) in the control group. Only Veterans recruited from the Providence VA Medical Center (PVAMC) will be allowed to enroll.

Inclusion Criteria:

1. At least eighteen (18) years old;

2. Chronic Low Back Pain - must be present for ≥ 6 months duration in the lumbar region, present more than half the days of the month, and on average be at a moderate level of severity in the last month (≥ 4 on the DVPRS scale of pain intensity from 0 (no pain) to 10 (worst pain imaginable).
3. At least one trial of physician recommended medication (i.e. acetaminophen, NSAIDS, skeletal muscle relaxants)
4. Pre-existing opioid and non-opioid pain medication must be non-existent or stable (medications have not changed for one month)
5. Be able to understand, read and write English.
6. If female and of childbearing age, agree to use acceptable birth control during the study treatment period (oral contraceptives, history of tubal ligation, history of a hysterectomy, or a reliable barrier method) during the study treatment period.

Exclusion Criteria:

1. Lifetime DSM-IV diagnosis of bipolar disorder, schizophrenia, or other chronic psychotic condition;
2. Current DSM-IV diagnosis of substance dependence for alcohol, sedative/ hypnotic drugs, stimulants, or cocaine;
3. Current cancer, infection, or inflammatory arthritis
4. Broken skin or other lesions in the area of the electrodes
5. Uncontrolled medical problems, such as diabetes mellitus, hypertension, pulmonary or airway disease, heart failure, coronary artery disease, or any other condition that poses a risk for the subject during participation.
6. Presence of metal in the cranial cavity
7. Holes in the skull made by trauma or surgery
8. Pacemakers, medication pumps, and other implanted electronic hardware;
9. Pregnancy

RECRUITMENT AND ENROLLMENT

Recruitment will occur through several methods. The main recruitment method will be through the Interventional Pain Clinic at the Providence VA Medical Center (PVAMC). The research staff will also educate other care providers about the study so they may inform their patients. Veterans may also self-refer for a screening to see if they are eligible. Additionally, we will advertise through flyers posted throughout the PVAMC and online posting sites (such as Craigslist, the PVAMC Research Service website, and the PVAMC Twitter and Facebook accounts). All advertisements will be reviewed and approved by the PVAMC IRB prior to release. Please refer to Appendix A for the language for these advertisements.

Written informed consent will be obtained prior to study related clinical screening or administration of any study measures or procedures. The consent process will be administered in person by a member of the study team who has received research ethics training. The study team member will assess the potential participant's comprehension of the consent form and will answer

all questions about the study. Participants will be informed that they may discontinue their participation at any time without penalty. Only Veterans will be recruited for enrollment.

Recruitment and Pre-screening Procedures:

Participants will be recruited through the Interventional Pain Clinic, at the PVAMC. The clinic care providers, who are also research personnel, will screen their patient's charts for study eligibility. They will make referrals by distributing study brochures to their eligible patients and provide them with a permission to contact form. This form includes the potential participant's permission to share the clinician's screening tool (which will be attached to the permission to contact form) with research staff.

If a study research assistant is available during clinic time, he/she will be introduced to patients interested in learning more about the study. If research staff is not available or potential participants do not have extra time on their clinic day, study staff will contact them by phone on the day and time requested on their permission to contact form to explain the study and answer any questions. All interested Veterans recruited will have discussions about the study either by phone or in person at the Interventional Pain Clinic, in an area of privacy. After study staff explains the study and answers any questions the potential participant has, if they are still interested, they will be scheduled for an appointment for the consent process and further assessment of eligibility. These appointments will be made for a meeting at the PVAMC (Building 1) or in the Neurorestoration Center Building 32, in a research exam room or office as assigned based on availability and/or convenience for the potential participant. The potential participant will be given clear directions about where the meeting will occur, what time and how to contact study research staff.

The consent process and further screening for study eligibility may be done on the same day as the care provider referral at the Interventional Pain Clinic, if the potential participant has time and makes this request.

In addition to this main recruitment method, research staff will educate other care providers at the Providence VAMC that also care for Veterans with chronic low back pain, (Example: Primary Care, Orthopedics, Physical Therapy, Cognitive Behavioral Therapist for pain, etc.) so they may inform their patients about the option of becoming involved in this study if they qualify. The IRB approved study brochure will be distributed around the hospital in waiting areas and on bulletin boards. It will also be posted on the hospital monitor so Veterans may self- refer. Screening for these Veterans will be done by research staff and reviewed with Dr. Burgess to determine eligibility.

Description of the informed consent process:

A Research Assistant (RA), trained interviewer, or Principal Investigator (PI) will obtain informed consent. Potential participants will have the study procedures explained in detail. As long as they continue to meet the study eligibility criteria, potential participants will be given as much time as they need to review the consent form, ask questions about the study, and make a decision as to whether or not to participate. A complete description of the study and full disclosure of the potential benefits, risks, and alternatives will be provided. Participants will be

required to sign the PVAMC IRB approved study consent form and HIPAA Authorization before completing any study procedures. A copy of the signed form will be given to participants to take with them. The original signed consent form will be kept in the principal investigators' study file and a copy will be made and sent for scanning into the Veteran's medical record. Participants will be told that they may refuse participation without any negative consequences, and that if they decide to participate, they will be free to withdraw from the study at any time.

The following information will be provided in the consent form:

1. The name of the study.
2. The name of the PI.
3. That the study involves research.
4. An explanation of the purpose of the study.
5. A statement of how long the study will last and the required number of visits.
6. A description of how the tDCS will be administered.
7. A description of tasks and protocol requirements.
8. A description of the questionnaires involved in the study
9. A discussion of the nature, risks, and benefits. (All risks involved with the study and use of study equipment will be clearly explained)
10. It will be made clear that the study is voluntary, and not required.
11. There will be time for all questions to be answered.

Subject Screening for Enrollment:

After signing the consent form and HIPAA authorization, potential participants will undergo further screening and collection of information with a trained research interviewer, designated by the principal investigators. The interviewer will collect demographic information (ex. age, gender, height, weight, racial/ethnic group, years of education, contact information) and further screen for study inclusion and contraindications of tDCS. (The screening assessments are further detailed under specific study procedures).

Screening is expected to take approximately one and a half (1 ½) to two hours (2). The principal investigator/s will make the ultimate determination of whether the participant meets all the enrollment criteria and is appropriate to enter the study. Participants that do not meet the study criteria will be informed that based on the information collected, it has been determined they are not appropriate for the current study. Appropriate referrals will be made to other health care providers, at the VA or to outside providers, if desired by the participant.

RESEARCH PLAN

After the potential participant signs the consent form, is screened, found eligible and states they are still interested, they will be enrolled into the study. The study includes a screening visit, ten (10) study treatment session visits on consecutive weekdays and a follow-up phone call, approximately six (6) weeks after the last study visit. The ten study visits will occur at the

PVAMC and will take approximately one (1) to one and a half hours (1 ½) hours. The follow-up phone call will take about one (1) hour. The total duration of this study for the participant is expected to be approximately eighteen (18) hours; this includes the consent process, screening and eligibility assessments, and ten research visits which will include the study treatment, tDCS, completion of study related questionnaires, and the follow-up phone call.

Half of the participants will receive only sham stimulation for all treatment days (days where tDCS is applied) and half will receive only active stimulation; this will be randomly assigned. Comprehensive measures of distress resulting from CLBP will be administered to assess both the short and longer term effects of tDCS treatment. Participants and research staff administering outcome scales will be blinded to active vs. sham tDCS.

Specific Procedures:

Questionnaires

Table 1, below identifies the schedule for when the study questionnaires will be used. All questionnaires will be done with assistance of blinded study personnel.

Pain Severity:

This study will use the 11-point numerical scale http://www.dvcipm.org/files/manuals-resources/dvprs.pdf http://www.dvcipm.org/files/manualsresources/dvprs.pdf for rating pain intensity developed by the Office of the Army Surgeon General Pain Management Task Force (2010). Zero (0) indicates no pain and ten (10) indicates the most severe pain. This will be administered on screening, before and after each treatment session, and at follow-up.

Pain Interference:

Two measures will be used to assess pain interference. First, the West Haven-Yale Multidimensional Pain Inventory (WHYMPI) (Kerns 1985) will be used as a measure of the chronic pain experience. The interference sub-scale will be used to measure perceived interference of pain in vocational, social/recreation, and family/marital functioning. Second, we will use the Rolland-Morris Disability Questionnaire (RMDQ) to assess disability specific to back pain (Roland & Morris 1983). The RMDQ is widely used and has acceptable psychometric properties (Roland & Fairbank 2000).

Emotional Distress:

Investigators will employ a battery of measures to determine the degree to which participants experience emotional distress resulting from pain. First, the affective sub-scale of the WHYMPI will be used to measure negative emotion related to pain. Second, the General Anxiety Disorder 7-item scale (GAD-7) will be used to assess general anxiety symptoms. Third, the Patient Health Questionnaire (PHQ-9) will be used to assess depressive symptoms (Kroenke 2001). The PHQ-9 is a quick self-report measure demonstrating reliability and validity in primary care settings

(Spitzer 1999). We will also include the short form of the pain anxiety symptom scale (PASS20) to measure fear and avoidance behavior related to pain (McCracken & Dhingra 2002). Lastly, we will assess pain acceptance with the Chronic Pain Acceptance Questionnaire-8 (CPAQ-8) (Fish et al 2010). This measure addresses the ability to experience ongoing pain but continue engaging in enjoyable daily activities that are not focused on avoiding or reducing the pain. This measure has good psychometric properties (Rovner et al. 2014)

Patient Expectation and Satisfaction:

We will assess treatment credibility and patient expectations for treatment success using the Credibility Expectancy Questionnaire (CEQ; Devilly & Borkovec 2000). The Client Satisfaction Questionnaire-8 (CSQ-8; Larsen, Attkisson, Hargreaves, & al., 1979), an 8-item scale, will be used at post-treatment to assess patient satisfaction with the treatment. This scale has acceptable psychometric properties (Nguyen, Attkisson, & Stegner, 1983).

Psychiatric History:

Drug related problems, exclusionary disorders, and other non-exclusionary psychiatric disorders will be assessed with a structured psychiatric interview, the Mini International Neuropsychiatric Interview (M.I.N.I.) for the DSM-IV. This is a validated interview designed to screen for Axis I disorders. Potential participants determined by the M.IN.I.to have lifetime diagnoses of bipolar disorder, schizophrenia, other chronic psychotic condition(s), and/or current drug or alcohol dependence will be considered screen failures.

Sleep Measure

An in-office assisted report of sleep will be used to assess quantity and quality of sleep throughout the ten testing days of the study. The questions used to assess sleep have been based on those used in the 1992 Carskadon Sleep-Wake Diary.

Table 1. Schedule of Assessments

	Purpose	Consent and Screen	First Day of Week One Session 1	Pre/Post Treatment Session 1-10	End of Week One and Two Session 5 & 10	Six Week Follow-up
Pain Severity Defense & Veterans Pain Rating Scale (DVPRS)	I, O	X	X	X	X	X
Pain Interference WHY-MPI RMDQ	O O		X X		X X	X X

Emotional Distress PHQ-9 (Depression) GAD-7 (Anxiety) PASS-20 (Pain related fear/avoidance) CPAQ-8 (affective dimension of pain)	 O O O O		 X X X X		 X X X X	 X X X X
Psychiatric History M.I.N.I.	 I	X				
Sleep Measure Sleep assessment	O		X	X	X	X
Patient Expectation and Satisfaction CEQ CSQ-8	 T T		 X X		 X* X* *(only session 10)	

Assessment instruments are used for the following purposes:
I= Inclusion criteria; T = Treatment Development Target Assessment; O = Outcome Measure

Links to the measures, when available:

DVPRS
WHY-MPI
RMDQ
PHQ-9
GAD-7
PASS-20
CEQ
CSQ-8

Study Visits

All participants will be clearly directed to the building and room where the study procedures will occur prior to each visit. All study visits will occur at PVAMC in Building 1 or at the Neurorestoration Center, Building 32, in a research exam room as assigned.

On the first day of treatment, prior to the tDCS treatment, females of childbearing age will be required to have a urine pregnancy test before any study procedures. The female participant will be brought to the PVAMC laboratory where the clinical laboratory staff will be handling and processing the participant's urine, do the pregnancy testing, and report the results as part of their daily clinical responsibilities. The pregnancy test will be done through the PVAMC laboratory according to their standard of practice. Research key personnel will not handle or have contact with the participant's urine for this pregnancy test. Participants are informed in the study consent form of this requirement to give permission for a pregnancy test to be involved in this study and

that the results will be recorded in their PVAMC medical record. Any participants that show a positive pregnancy test will be considered a screen failure.

Participants will be asked to complete the DVPRS, WHY-MPI, RMDQ, PHQ-9, GAD-7, PASS, CPAQ-8, CEQ, CSQ-8, and the Sleep Measure. This will provide a baseline measure in regards to the sensory/perceptual component of their pain, the degree to which pain interferes with daily activity, and the emotional component of their pain.

Prior to this and each study treatment, designated research staff will assess the skin on the participant's scalp where the electrodes will be placed to assure there are no lesions, cuts, or exclusionary skin disorders. Participants will be positioned for optimal comfort on a chair, recliner, or stretcher. Designated trained research staff will attach the electrodes to the participant's scalp (participants will not need to have any hair shaved) and apply the flexible rubber headband to keep them in place (see detail below). Participants will be educated that research staff will be monitoring them continuously through a non-recording closed-circuit camera from another room or he/she will be physically present in the room to assess if they need anything or want to stop the tDCS.

The participant will then receive either the sham or active tDCS stimulation based on their random group assignment for twenty minutes (tDCS details are below). Following tDCS stimulation, only the DVPRS will be repeated. This measure will be used to determine whether immediate pain relief following stimulation occurs. Lastly, in order to monitor the effectiveness of the blind, participants will be asked to guess which treatment, active or sham, they received.

On subsequent treatment days, the DVPRS will be repeated before and after stimulation and the Sleep Measure will be repeated before stimulation.

At the end of the first week of treatment, session five, in addition to the DVPRS and the Sleep Measure, the WHY-MPI, RMDQ, PHQ-9, GAD-7, PASS, and CPAQ-8 will be repeated.

During the second week, the DVPRS will again be administered before and after each treatment, and the Sleep measure will be repeated before stimulation

On the final day of treatment, in addition to the DVPRS and the Sleep Measure, the WHYMPI, RMDQ, PHQ-9, GAD-7, CEQ, CSQ-8, PASS, and CPAQ-8 will be repeated.

Follow-up assessments will occur by phone approximately six (6) weeks after the last tDCS treatment session and will consist of the same measures as session ten.

tDCS details:

Equipment used for tDCS Intervention, the Neuroconn DC-STIMULATOR PLUS, is a micro-processor-controlled constant current source. tDCS is a non-invasive procedure in which a device sends a small Direct Current (DC) across the scalp to modulate brain function. A lowlevel current from the positive electrode, anode, is sent to the negative electrode, cathode. When the extremely low level current passes from the anode to the cathode, it may simultaneously increase the activity of the brain by the anode and decrease the activity of the brain near the cathode. The DC-stimulator meets the highest safety standards thanks to (hardware- and software-based) multistage monitoring of the current path. It continuously monitors electrode impedance and it can detect insufficient contact with the skin and automatically terminate stimulation to reliably prevent participant injury.

The FDA recognizes the tDCS device as a non-significant risk device. During each treatment session, tDCS will be applied to the scalp using a Neuroconn DC- Stimulator Plus (Figure 1).

Figure 1. tDCS device

Stimulation will be applied to the participant's skull using metal electrodes seated in a flat, slightly perforated rectangular sponge pocket. The sponges will be soaked in normal saline (0.9% NaCl) and affixed to the head on intact skin (after the scalp skin is cleaned with an alcohol prep pad) and held in place with a custom tDCS specific rubber headband. One set of sponges will be used for each participant. Standard conductive water based gel (Spectra 360 electrode gel) will be applied to the sponge (between the scalp and the sponge) only if the impedance is found not to be optimal, to improve current flow. In this experiment, only 1 stimulating electrode and 1 reference electrode will be used. The investigators will target the dorsal anterior cingulate cortex by placing the stimulating electrode at FC_1 on the 10-20 EEG system (see Figure 2). The reference electrode will be placed on the contralateral supra-auricular point, at T_3 (see Figure 3). Point T_3 will be located immediately above the superior tip of the participant's pinna. Point FC_1 will be located via scalp measurements: 50% of the way from the participant's nasion to inion will be used as reference point C_z (see Figure 2), 33% from the nasion to inion will be used as point F_z, and 50% of the way from T_3 to C_z will be used as C_3. FC_1 will be 50% of the way from C_3 to F_z. Active tDCS, i.e. anodal or cathodal, will be applied during the session. The device will deliver a maximum of 2 mA (2.55 mA/cm2) of direct current stimulation for twenty (20) minutes which is controlled by a timer on the device.

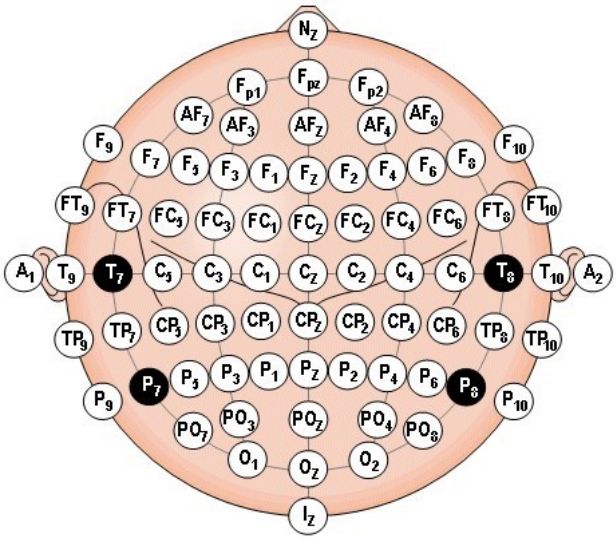

Figure 2. 10-20 EEG System

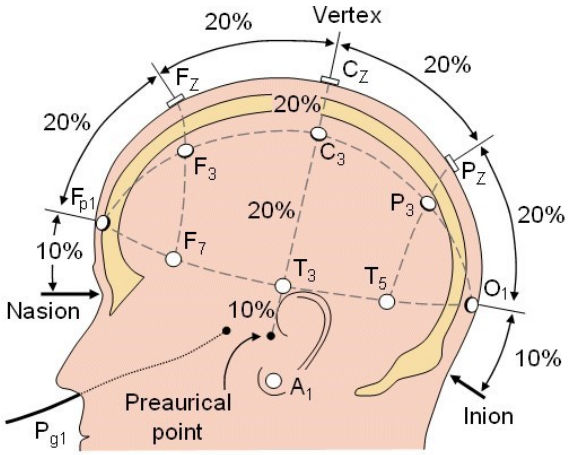

Figure 3. 10-20 EEG System

In the sham condition, the current paradigm will consist of 40 seconds of stimulation at 1mA and then 19 minutes and 20 seconds of stimulation averaging no more than 0.002mA This procedure allows for participants to detect the associated tingling sensation at the beginning of the session, making participants more likely to believe that they are receiving active stimulation and the short duration is not expected to have any effect on brain function.

HUMAN SUBJECT PROTECTION

Potential Risks and Discomforts

There are minimal risks to be incurred from participating in this study. Specific risks related to the clinical and cognitive assessments (study questionnaires) and tDCS are described below. Participants may be uncomfortable sitting or lying for an extended period of time on the chair, recliner or stretcher due to their CLBP.

Risks and discomforts due to Clinical and Cognitive Assessment Administration:

There are several questionnaires that the participant will be asked to answer. The time it takes to answer these questions may create frustration or fatigue. Answering the clinical symptom rating questions may involve sensitive information that could cause emotional reaction, embarrassment or discomfort. Previously undisclosed or unknown mental health problems may be identified,

Risks due to tDCS:

There is some inherent risk with tDCS. Mainly there is a risk of skin irritation where the electrodes are attached to the scalp, which in the literature has been mostly limited to transitory redness. No toxic effects have been found, and the procedure carries few risks (Brunoni, et al., 2012). At the levels we are proposing, only a few publications report minor injuries, and the stimulation is widely considered to be "safe" (Bikson, et al., 2009). In rare cases, when skin around stimulation sites was non-intact, or when the stimulation was delivered for a long time without proper conductive solutions being applied to the electrodes, a few minor burns and skin lesions have been observed (Frank, et al., 2010). If electrodes/sponges are placed over preexisting skin lesions, such as vascular moles and angiomas there may be a greater conductance than the surrounding skin, increasing the risk of irritation or possible burns. Care is thus taken to exclude potential participants who exhibit broken or marked skin near the sites of the electrodes. The electrodes in this study are soaked in normal saline. A study using the same amperage proposed in this protocol found no mood or cognitive changes due to tDCS (Iyer, et al., 2005). Transient, very rare post-tDCS effects have been found to include mild headaches, nausea, and insomnia (Poreisz, et al., 2007).

PROTECTION OF THE SUBJECT

Participants will be reminded that they may stop participating in the study at any time for any reason without affecting their VA health care or relationship with PVAMC.

Participants will be encouraged to take breaks when needed. They will be reminded that they may refuse to answer any questions on the study questionnaires and they may stop the tDCS treatment session at any time.

Management of Risk due to due to Clinical and Cognitive Assessment Administration

Dr. Greenberg and/or Burgess will be available to address any mental health concerns and assist in appropriate referrals as needed. As noted above participants may refuse to answer any questions and take breaks as needed.

Management of Risks due to tDCS.

Further Background information and precautions related to risk

Direct Current (DC) polarization has been applied unilaterally to the primary motor and dorsal prefrontal areas in many studies over the past decade (Wassermann, 2008) with no reports of adverse effects attributable to effects on the central nervous system. The proposed stimulation intensity in this study is similar to the stimulation intensity used in previous protocols as also performed at the NIH (and for which the risk determination from the FDA was requested). No adverse side-effects have been reported in these previous studies with the proposed stimulation settings. The proposed intensity level is therefore at the level at which we will expect to find effects of tDCS on our behavioral output measure, but without causing adverse side-effects. In a study measuring thermal effects of tDCS using a MRI-derived finite element human head model conventional rectangular-pad (7 times 5 cm2) and HD-tDCS using the ring (4 times 1) electrode configurations were compared using a bio-heat model. The results indicate that clinical tDCS

does not increase tissue temperature and the 4 x 1 configuration leads to a negligible increase in scalp temperature (Datta et al., 2009). In safety studies conducted at City College of New York (CCNY) and during usage at the National Institutes of Health (NIH), sets of these electrodes did not cause skin problems more serious than tingling and transient redness when applied to the skin of the arm with current densities up to 2.56 mA/cm2 and durations of up to 22 minutes (Dr. Biksom, personal communication). It was also found that cathodal current produced the most skin irritation. However cathodal stimulation will be of crucial importance to our study design as we hypothesize that our target brain areas may be overactive, and hence require suppression. During cathodal stimulation we will take extra precautions that consist of instructing the participants to advise the research staff of any discomfort during testing, inspection of stimulation sites as needed and immediate discontinuing stimulation if discomfort occurs.

The tDCS device that will deliver the direct current is adjustable in both intensity as well as duration of stimulation. In addition, the device will be 9V battery-driven to function as a constant current stimulator with a maximum output in the milliamps range with absence of the risk of sudden large intensities of electrical current that could occur with an electrical driven device.

Prolonged passage of direct current across metallic electrode (where electrons from the stimulator are converted to ions carried through the body) can produce undesired electrochemical products such as pH changes. The sponge pocket will act to physically separate, and thus buffer, the skin from electrochemical changes. The normal saline used on the sponges assists in preventing burns. In addition, electrodes/sponges will not be placed over cuts, or skin lesions such as vascular moles and angiomas that might have greater conductance than the surrounding skin. One set of sponges will be used throughout the study for each participant Electrodes will be held in place by using special head bands made of flexible rubber.

All participants will be carefully screened prior to tDCS for contraindications to tDCS (see exclusion criteria). At least one PI will be available on an immediate basis for all study treatment sessions.

tDCS will be administered by the tDCS Operator - a trained and qualified individual supervised the principal investigators to deliver, or assist in delivery of, tDCS. Training includes the knowledge of safety considerations and precautions associated with tDCS.

The tDCS operator will:

a) Assess the participants' scalp skin where the electrodes will be placed to assure it is intact,
free of lesions, cuts or exclusionary skin disorders.

b) Prepare and position the electrodes and tDCS device on the participant for accurate brain
stimulation according to the protocol prior to initiation of stimulation.

c) Operate the hardware associated with the tDCS device to assure the level of current and
amount of time is accurate per protocol.

d) Administer the tDCS, at the parameters established by the tDCS Attending Physician as
per identified in this protocol.

e) Assess the participant's mental status and general clinical condition before and after tDCS

to assure the safety of the participant to have tDCS and the safety of the participant to return home.

f) Monitor the participant during the tDCS session to assess for potential occurrence of adverse events.

g) Make routine adjustments to the placement of the device as required and consistent with product labeling (e.g., to ensure contact between participant's head and electrode) during the tDCS session. The tDCS Operator may not independently make any revision to pre-determined stimulation dose or electrode position parameters prescribed by the study protocol.

h) Determine if tDCS should be interrupted or terminated (e.g., participants express increasing discomfort to their skin under the electrodes; participants show signs of discomfort or other stress; participant wants to discontinue study procedures).

i) Take action in accordance with established VA regulations in case of adverse events, for example: he/she will seek immediate medical attention for the participant if necessary; if there is any doubt about the mental or physical status of a participant after testing he/she will consult with the available study physician. He/she will document and report all adverse events (e.g. skin lesion or significant skin discomfort) to the principal investigators. A study physician will evaluate the participant and make a recommendation for immediate or follow-up care if required. Telephone or in-person follow-up will be arranged as needed. Any participant judged on clinical grounds to have suffered adverse effects will thus be evaluated and treated as necessary and withdrawn from the study.

j) When not in use, assure the tDCS machine, electrodes, sponges, conductive gel, alcohol prep pads and normal saline are maintained in the secure location as assigned to Drs. Burgess and Greenberg in Building 1 or 32, in a locked cabinet in a lockable room.

Management of Risks to Confidentiality:

This study will be conducted in compliance with Good Clinical Practice procedures. Strict standards of confidentiality will be maintained. Precautions will be taken to prevent disclosure of information to unauthorized parties.

All paper records, forms and data will be stored in secure files to which only members of the investigative team will have access. Computer records will be protected by standard measures that limit access of the data to designated trained research project personnel.

This research data will include participant information that may be of a sensitive nature. All patient data will be stored in locked files in lockable offices. Computers with subject data will be password protected and encrypted to ensure confidentiality of patient records. Specifically: (1) Data sheets will be stored in one of the Principal Investigators' locked files in a locked office as a assigned at the Providence VA Medical Center); (2) Data will be entered in coded form; (3) Data will be stored in computer files protected from unauthorized access by passwords; (4) Information that might potentially allow an individual participant to be identified will not be allowed in any publications, or reports sent to individuals outside the study; and (5) All

employees who are to handle data will be certified in Good Clinical Practice and Human Subjects Protection Training in confidentiality policies and procedures.

Adverse Event Reporting:

Throughout the study, participants will be monitored by the research assistant and research staff for adverse events. The research team will meet bimonthly and/or as needed to review the logistics of the study and review all adverse events and problems. The PI's will review all adverse events (AE) and serious adverse events (SAE) as soon as reported and will submit reports as required by the SOP's (Standard Operating Procedures) of the Providence VA.

Adverse events (AE) will be defined as any reaction or side effect that occurs during the course of the clinical trial. A new illness, symptom, unfavorable or unintended sign, or worsening of a pre-existing condition or abnormality will be considered an AE. Serious Adverse Events (SAEs) will be defined as any fatal event, any immediately life-threatening event, any permanent or substantially disabling event, and any event that requires or prolongs inpatient hospitalization. Any unexpected event that suggests a significant hazard, contraindication, side effect or precaution will also be reported. One of the PI's will promptly report all SAEs to the PVAMC IRB within twenty- four (24) hours by telephone, and follow with a completed SAE Form within two (2) days. The completed SAE Form will include demographic information, a narrative explanation of the event, and photocopies of any relevant source documents from the participant's case report forms. As a result of an AE or SAE the PI's will address whether there is a need to re-design or amend the protocol or a need to change the description of risk, either in the consent form or in the protocol

Medical Care for Research-Related Injuries

In the event of research-related injuries to participants in this project, medical care related to that injury will be provided at no cost to the participant.

Potential Benefits

This study is designed to measure the potential benefits of tDCS for treating pain. This is an investigational study and therefore we cannot guarantee that patients will indeed experience a reduction in symptoms of their chronic low back pain. Participating in this study, however, may serve to benefit advances in understanding chronic pain, potentially leading to future improvement in treatments.

Risk-Benefit Ratio

Furthering knowledge regarding the brain mechanisms underlying the affective component of the chronic pain experience may provide significant benefit in developing alternative effective treatments for chronic pain. The approach taken in this research may provide beneficial treatment for this debilitating condition. Additionally, transcranial direct current stimulation, or tDCS, is classified by the FDA as a minimal risk technique. Therefore, we believe that the potential benefits of this study greatly outweigh the potential risks that may occur as a result of participating in this study.

DATA COLLECTION AND SECURITY:

Excel, SPSS and Word will be used for data collection, licenses for this software is held by the VA. Participant data collected for this study will be stored and processed on passwordprotected VA desktop computers. Paper files will be stored in a lockable office in a PI's locked file at the PVAMC as assigned. The participants' demographics, screening questionnaires, consent forms and HIPAA authorizations will be stored, separate from study data files

All study data will be labeled only with the participants' unique study code, which will be assigned at random. Only the Principal Investigators and their designated research staff will have access to the unique code linking the research data to the participants' identifiers. This link will be stored separately at the PVAMC in a PI's lockable office in a locked file as assigned.

The study data will be stored on the Shared Research drive (P-drive) at the Providence VA Medical Center in the restricted folder: \\ R04pronas21\research_protocols\ Burgess \ tDCSCLBP-R. No VA data will be removed from the PVAMC site.

Records will be maintained in accordance with the Department of Veterans Affairs Record Control Schedule 10-1. The PHI will be destroyed per the Department of Veterans Affairs Record Control Schedule 10-1.

The PI's (Dr. Greenberg and Burgess) will be responsible for assuring that VA access accounts are terminated when a user no longer needs access. In the event that a theft, loss, or other unauthorized access of sensitive data or storage devices occurs, as well as non-compliance with security controls, the Information Security Officer (ISO) will be notified immediately. Research staff will carry out any necessary procedures given by the ISO in order to resolve the situation.

Data collected from this study will be used for research purposes. Information that might potentially allow an individual participant to be identified will not be allowed in any publications or reports or sent to individuals outside the study. Information that could potentially allow an individual participant to be identified will not be shared with any researchers who are not directly involved with the study.

DATA ANALYSIS

Data analysis will be conducted using standard statistical software, SPSS, the license is held by the Providence VA. Data will be analyzed through linear models including (M)ANOVA, repeated measures analyses and mixed linear model procedures to deal with correlational effects. This will be followed by appropriate post-hoc analyses comparing specific conditions. In order to maintain anonymity in restricted data files participants will be only listed with their unique identification code. Clinical rating scales will be scored as they are in clinical use. Word and Excel will also be used, PVMAC hold licenses for these programs.

There is no power analysis as this is an exploratory study.

STUDY LOGISTICS

Training of Research Personnel

Prior to initiation of the study all research personnel will be trained in the specifics of this research project according to their role. Research personnel responsible for administering

assessments and questionnaires will be trained by the PIs and Co-PIs. Ongoing training will occur as needed, especially if the study is amended and for review of the logistics and progress of this project.

All research staff will have completed research ethics training; including data management and procedures for maintaining data confidentiality and safety before being allowed to work on the project.

Urine pregnancy tests will be done through the VA laboratory according to their standard operating procedures.

Location of Study

Recruitment will occur at the Interventional Pain Clinic. The study assessments and treatment will be conducted at PVAMC, in one of the PI's areas as assigned in Building 1 or Building 32. Renovations to space in these areas are pending. Prior to the scheduled study visit participants will be clearly informed what building and office their study session will occur. Study staff contact information will be provided so participants may call with questions about the location.

FUNDING AND COMPENSATION

Material Inducements

Compensation for time and effort will be offered for the measures administered in this study. Participants will receive $100 worth of gift cards as compensation for participation if they complete all 10 sessions of tDCS treatment. If the participants withdraw from the study before finishing, they will receive $10/session for each session in which they participated regardless if they were able to complete the full session.

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Appendix A: Social Media Recruitment

A. Language for Online Posting Sites (i.e. Facebook and/or Craigslist) – Volunteers Needed for a Study of Veterans with Chronic Low Back Pain We are looking for Veterans with chronic low back pain to participate in an 11 day research study at the Providence VA Medical Center. This study is looking at whether or not small amounts of electricity applied to the head may be able to change the way one feels about their chronic pain.

The study involves 11 study visits at the PVAMC, the first to see if you are eligible, followed by 10 study treatments. A follow-up phone call is also placed several weeks after the study treatments are completed. During study visits, participants will undergo a low level electrical current through their head for 20 minutes and will be asked to answer questions about pain, mood, sleep, and well-being. Some participants will not receive the actual treatment and participants will not know if they are assigned to this group.

Participants will receive gift cards of up to $100, $10 value for every treatment session attended, for their time and effort.

For your own security, please do not comment with any of your personal or health information, call (401) 273-7100 ext. 6256 or ext. 6221 and arrange for a secure means to share such information in response to this post.

B. Language for Twitter (140 character limit)

Are you a Veteran with chronic low back pain? You may qualify for a research study at PVAMC. Call 401-273-7100 ext. 6256 for more info.

Appendix B- inclusion of de-identified data from Butler Hospital

There is an IRB approved parallel study at Butler Hospital, in Providence RI. De-identified data from this study will be included in the analysis of this study. Sharing of this de-identified data has been approved by the Butler IRB. This de-identified data will be entered into the study's data capture excel spreadsheets stored on \\R04pronas21\research_protocols\ Burgess \ tDCS-CLBPR and analyzed by the study statistician and research staff.
The Investigator will send a copy of the Butler data to his VA email account. The Investigator will then upload and co-mingle the Butler data with the existing data located above. There is no expectation of return of the data.
There is no additional software or web access needed.
The data flow is amended to include the additional data from Butler detailed above.

There will be no hard drives on this study.
The storage location will remain the same.
There will be no removal of sensitive data from the VA environment.
No storage of data outside the VA environment.
The data transmission will be an email of de identified data one way one time to append the data base at the VA Medical Center.
No shipping will be required
No data return is expected.