IRB # 1411-003

BUTLER HOSPITAL
INSTITUTIONAL REVIEW BOARD

BUTLER HOSPITAL IRB NEW SUBMISSION FORM

For: (check one)

☑ **Protocol for Research Involving Human Subjects:** Complete Sections 1-4 & 6-9

☐ **Waiver of Authorization for use of Protected Health Information (PHI) Study**: Complete 1, 5, 6 & 7

☐ **Waiver of Authorization for use of Protected Health Information (PHI) Preparatory to Research:** Complete 1, 6 & 7

Protocol Status: ☑ New ☐ Renewal -or- **Authorization Waiver Status:** ☐ New ☐ Renewal

1.) TITLE OF PROJECT: 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

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Funding: (Source, PI): Internal Funding
Duration of Project: 1 year **Duration for Individual Subjects: (**if waiver: n/a**)** 2 months
Specific Location(s) of Project: Butler Hospital

Check if applicable:

☐ **Investigational New Drug/Device (IND/IDE#** _____)
☐ **Use of Radioisotopes**
☐ **Student Research (Student** _____)
☐ **Minors** ☐ **Fetuses** ☐ **Intellectually disabled** ☐ **Abortuses** ☐ **Pregnant Women**
☐ **Prisoners** ☐ **Special racial/ethnic group (Specify_____)**

Check if requirements have been met (submit written explanation if "no"):

Have all investigators completed research ethics training? ☑ **YES** ☐ **NO**
Have all investigators completed FCOI training in the past 4 years? ☑ **YES** ☐ **NO**
Have all investigators completed FCOI Disclosure forms? ☑ **YES** ☐ **NO**

ATTENTION:
Before completing this protocol, go to the Butler IRB Forms website:
http://www.butler.org/irb/forms.cfm
Download the most recent version of this and any other needed IRB forms and consult the **IRB Guidelines** for updated directions.

Date most recently revised (m/d/y): 03/03/2015
Protocol Version (if applicable): 5.0

2.) Description of Study

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 meet all the inclusion and exclusion criteria.

A. 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 twenty (20) patients in a controlled design.

Hypothesis: Acute Effect

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), PASS-20, 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

Aim 2 To test the longer term effects of active vs. sham cathodal (inhibitory) tDCS over dACC in the same twenty (20) patients in a controlled design.

Hypothesis: Longer Term Effect

Hypothesis 2.1

Distress associated with pain as measured by the WHYMPI (affective subscale) and PASS-20 will remain decreased at follow-up.

Hypothesis 2.2

Pain-related avoidance and disability measured on WHYMPI (interference subscale), PASS-20, and RMDQ will remain decreased at follow-up.

Hypothesis 2.3

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

B. 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.

C. Experimental Method

C1. Brief Description of Subjects

Participants will be aged over 18 years old with a diagnosis of chronic low back pain based on the inclusion criteria (see below) by a referring physician. Participants will be of any racial or ethnic group and of either sex. A questionnaire will be administered to screen for possible contraindications for tDCS (see exclusion criteria). We will consent up to thirty (30) volunteers with a goal of enrolling twenty (20) participants, ten (10) in the treatment group and ten (10) in the control group.

C2. Study Design

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 Butler Hospital and will take between two (2) to two and half hours (2 ½) hours. The total duration of this study for the participant is expected to be up to approximately twenty- four (24) 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.

C3. Specific Procedures or Treatments

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.

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 for rating pain intensity developed by the Office of the Army Surgeon General Pain Management Task Force (2010). 0 indicates no pain and 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).

Pain Acceptance: 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)

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). Lastly, we will include the short form of the pain anxiety symptom scale (PASS-20) to measure fear and avoidance behavior related to pain (McCracken & Dhingra 2002).

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 (MINI). This is a validated interview designed to screen for Axis I disorders. Potential participants that are determined by the MINI to have lifetime diagnoses of bipolar disorder, schizophrenia, other chronic psychotic condition(s), and/or 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
Pain Acceptance CPAQ-8	O		X		X	X
Emotional Distress PHQ-9 (Depression) GAD-7 (Anxiety) PASS-20 (Pain related fear/avoidance)	O O O		X X X		X X X	X X X
Psychiatric History MINI	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

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WHY-MPI
RMDQ
CPAQ-8
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 Butler Hospital in a research room.

On the first day of treatment, prior to the tDCS treatment, females of childbearing age will be required to have a urine pregnancy test (hCG dipstick) before any study procedures. The test will be administered by a trained member of the research staff overseen by Dr. Greenberg or another licensed physician. 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, CPAQ-8, PHQ-9, GAD-7, PASS, 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, CPAQ-8, PHQ-9, GAD-7, and the PASS, 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 WHY-MPI, RMDQ, CPAQ-8, PHQ-9, GAD-7, CEQ, CSQ-8, and the PASS, will be repeated.

Follow-up assessments will occur by phone approximately six (6) weeks after the last tDCS treatment session and will consist of these 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 low-level 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.

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.

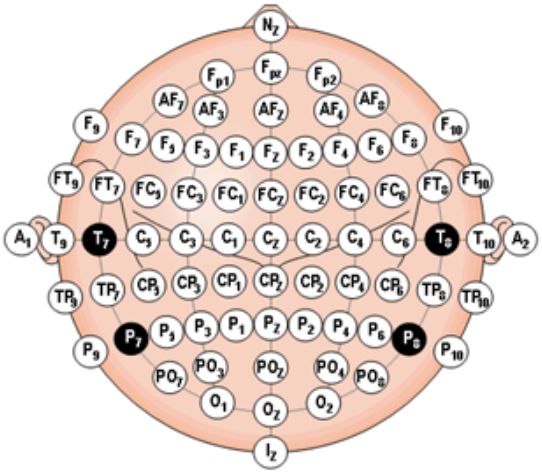

Figure 2. 10-20 EEG System

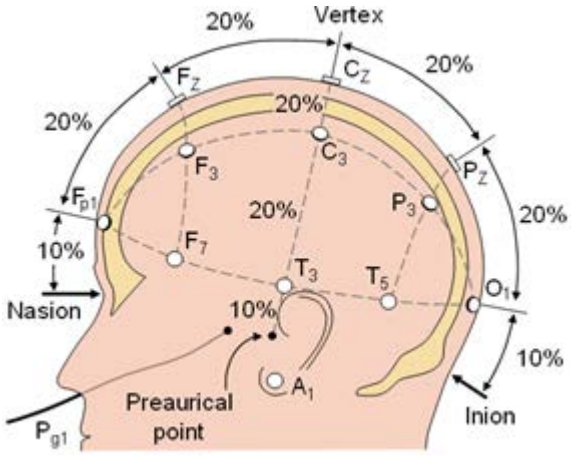

Figure 3. 10-20 EEG System

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.

C4. <u>Data Analysis</u>

The PI(s) will be responsible for and supervise data collection and data management. Data will be stored in a locked cabinet in the PI's office. Data analysis will be conducted using standard statistical software including SPSS and R. 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 data files participants will be only listed with their unique identification code. Data backup of these files and hard copies of data capture forms will be kept in locked files to which only authorized study personnel will have access. Descriptive data will be provided for all participants (e.g., mean age, sex, education, etc.). Clinical rating scales will be scored as they are in clinical use. There is no power analysis as this is an exploratory study.

D. <u>Material Inducements</u>

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Compensation for time and effort will be offered for the measures administered in this study. Participants will receive $60 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 $6 per session for each session in which they participated regardless if they were able to complete the full session**.**

E. 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 at Butler Hospital by a trained member of the research staff under the supervision of a licensed physician.

3) Human Subjects

A. Subject Population *(include number; gender; age; diagnosis; inpatient vs. outpatient; physical health; inclusion/exclusion criteria; rationale for use of special groups)*

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 thirty (30) volunteers with a goal of enrolling twenty (20) participants, ten (10) in the treatment group and ten (10) in the control group.

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

B. Recruitment and Consent Procedures

Recruitment will primarily take place through referral from Butler Hospital clinicians or community providers. Advertisements will also be posted at Butler Hospital and online. See appendix for a text of these advertisements. Written informed consent will be obtained prior to clinical screening or administration of any measures or procedures. The consent process will be administered in person by a member the study team who has received research ethics training. The study team member will assess whether the potential participant understands the study procedures, and will ensure that all questions related to the study are answered. Participants will be informed that they may discontinue their participation at anytime without penalty.

After signing the consent form, 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 up to one and a half hours (1 ½). 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.

C. Potential Risks

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 and to avoid abrading the skin prior to placing the electrodes (Loo et al. 2011). 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). In a prior study conducted by Drs. Greenberg and Mariano, eight of 40 participants reported sensations of itching, tingling, or burning under the tDCS electrodes; one participant reported mild dizziness. These sensations were consistent with those commonly reported for tDCS (Brunoni, et al., 2012). Less well-studied is the possibility of negative effects of tDCS on cognition and mood. A study using the same current amplitude as proposed in this protocol found no mood or cognitive changes due to tDCS, but this was with a single stimulation session (Iyer, et al., 2005). Several studies have used multiple sessions of tDCS of different brain regions successfully to reduce pain intensity from acute pain, neuropathic pain, and chronic pain from fibromyalgia (Antal, et al., 2008; Lefaucher, et al., 2008; Fregni et al. 2006) without significant adverse effects. Another potential concern is the risk of an undesired synergistic effect between a participant’s existing medication and tDCS. There are some reports in the literature of isolated instances of hypomanic or manic symptoms, typically noted with a longer treatment course than proposed in the current study or in patients with pre-existing bipolar diagnoses (Brunoni, et al., 2013; Galvez, et al., 2011) diagnosed bipolar disorder is an exclusion criterion for the present study. Nonetheless, comprehensive clinical studies quantifying the risk more precisely are clearly lacking. For the present study, participants will be closely monitored throughout the study to assess for any such effects. Participants will also be specifically instructed to tell the research staff if they notice an unwanted change in mood.

D. Protection of the Subject *(include: D.1. measures to minimize potential risks; D.2 measures to ensure confidentiality; D.3. data safety monitoring plan)*

Participants will be reminded that they may stop participating in the study at any time for any reason with no adverse consequences to health or future relationships with Butler Hospital or Brown University. 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.

D.1. Measures to Minimize Potential Risks

D.1A Management of Risk due to due to Clinical and Cognitive Assessment Administration

At least one of the MD investigators 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.

D.1B Management of Risks due to tDCS.

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 (7x5 cm^2) electrodes were found not to increase tissue temperature using a bio-heat model (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/cm^2 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 by the principal investigators to deliver, or assist in delivery of, tDCS. Training includes the knowledge of safety considerations and precautions associated with tDCS.

Participants will be closely monitored throughout the study to assess for any adverse effects on cognition or mood. Participants will also be specifically instructed to tell the research staff if they notice an unwanted change in mood during the course of treatment.

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 participants 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 Butler Hospital 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 Dr. Greenberg in a lockable room.

The experimenter will closely observe participants for signs of skin burns, discomfort, or other stress. Participants will have the option of discontinuing the study at any time and will be explicitly instructed to inform the experimenters immediately if they experience any discomfort. The experimenter will inform the supervising physician about any participant who has significant skin discomfort or a skin lesion after current delivery. If there is any doubt about the mental or physical status of an individual after testing, the principal investigators (or other supervising physician) will evaluate the participants and make a recommendation for follow-up care if that is required. Telephone or in-person follow-up will be arranged as needed. Any participant judged on clinical grounds to have been injured as a direct result of participation in this research will be offered emergency medical treatment by Butler Hospital paid for by research funds, except for costs that are covered by your insurance or governmental programs, and withdrawn from the study.

D.2 Management of Risks to Confidentiality

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.

D.3. Data Safety Monitoring Plan

Specific aspects of the data safety monitoring plan are: (1) Data sheets will be stored in one of the Principal Investigators' locked files in a locked office; (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.

Only information relevant to the protocol will be recorded. Personal Health Information (PHI) collected as part of the study protocol is shared only with the collaborative site on the project and is shared in de-identified form only.

E. <u>Potential Benefits</u>

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.

F. 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.

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5) STUDY RATIONALE: ***(complete for studies where only waiver is requested):***

6) CRITERIA FOR WAIVER OF AUTHORIZATION FOR USE OF PROTECTED HEALTH INFORMATION (PHI)

6A. Does the requested use of PHI involve more than minimal risk to privacy?

☐ **YES** ***[if " YES," project is not eligible for PHI Waiver]***

☑ **NO** ***[if "NO," address 1-3 below]***

Plan to Protect Patient Identifiers from Improper Use and Disclosure:

Date most recently revised (m/d/y): 03/03/2015
Protocol Version (if applicable): 5.0

a. Any on site electronic file containing PHI is password protected.
b. All subjects will be assigned a number to which they are referred so that only their number is associated with their data file.
c. All paper files containing subject responses are kept under lock and key.
d. Patients will not be personally identified in any publications or reports of this research.
e. Only trained research staff will have access to patient charts and data.
f. Only information relevant to the protocol will be recorded.
g. The master list and copy containing subject names and study numbers will be password-protected on computer equipment in a locked office.

Plan to Destroy Identifiers or Justification for Retaining Identifiers:
Identifiers will be retained so that they may be used for data analysis in this protocol and future
investigations.

Assurances that the PHI will not be Re-used or Disclosed:
PHI collected as part of the study protocol is shared only with the collaborative site on the project and is shared in de-identified form only.

6B. Could the research be practicably conducted without a waiver?

☐YES ☑NO

6C. Could the research be practicably conducted without access to and use of the PHI?

☐YES ☑NO

6D. PHI is only needed for activities preparatory to research

☐YES ☑NO

7) DESCRIPTION OF NEEDED PHI

Name, date of birth, gender, education level, ethnicity, telephone numbers, address, address, clinical diagnoses, treatment history, medical history, clinical rating scores, cognitive test results.

8) ADVERTISEMENTS

Transcranial Direct Current Stimulation (tDCS)
for Chronic Low Back Pain Research Study

We are studying a new device for treating chronic low back pain (CLBP) and are enrolling adults age 18+ in a clinical research trial. If you have been diagnosed with CLBP by a physician for at least 6 months, have tried at least one physician-recommended pain medicine, and have no current diagnosis of substance dependence, you may be eligible to participate. We will use a method for stimulating the brain, called transcranial Direct Current Stimulation (tDCS), to attempt to change the way you feel about your pain.

The tDCS device uses a small electric current applied through removable electrodes placed on your scalp while awake. We will not need to shave any hair. Study participants will be randomly assigned to receive active or placebo tDCS, while following their regular health routine.

- The study involves 10 visits to the Butler Hospital campus over a 2-week period with a follow-up phone call approximately six (6) weeks later.
- Compensation up to $60 is available for eligible study participants.

Eligibility

- Adults (18+) with a history of chronic low back pain made as a clinical diagnosis
- Any pre-existing pain medication must be stable for at least one month
- No lifetime DSM-IV diagnosis of bipolar disorder, schizophrenia, or other chronic psychotic
- conditions
- No current cancer, infection, or inflammatory arthritis
- No metal in your head or holes in your skull from trauma or surgery
- No implanted pacemakers, pumps, or other electronic hardware

If you are interested in learning more about Transcranial Direct Current Stimulation (tDCS) for Chronic Low Back Pain Research Study, please call (401) 455-6610 or go to www.butler.org/XXXX.

Please provide your name, telephone number, and a good time to reach you. Please do not include any other information. When you are done, press submit. A member of the research team will contact you soon.