Medical University of South Carolina
Protocol

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Study Title: **Effects of transcranial Direct Current Stimulation and Brief Cognitive Intervention on Pain Tolerance**

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A. SPECIFIC AIMS

List the broad, long-term objectives and the goal of the specific research proposed, e.g., to test a stated hypothesis, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, or develop new technology.

This study aims to evaluate the effectiveness of transcranial direct current stimulation (tDCS) and a brief cognitive intervention in increasing pain tolerance. Specifically, this study will determine whether healthy subjects will indicate greater pain tolerance to a heat stimulus following a single 20-minute session of anodal vs. cathodal tDCS (compared to sham tDCS). This study will also test whether providing one of four cognitive pain-managament interventions (conducted during the tDCS session) will result in even greater pain tolerance among subjects who also received tDCS .

B. BACKGROUND AND SIGNIFICANCE

Briefly sketch the background leading to the present application, critically evaluate existing knowledge, and specifically identify the gaps that the project is intended to fill. State concisely the importance and health relevance of the research described in this protocol by relating the specific aims to the broad, long-term objectives. If the aims of the study are achieved, state how scientific knowledge or clinical practice will be advanced.

Recently, the use of low amplitude direct current stimulation of the human cortex has received attention as a possible treatment for pain (Been et al, 2007). This technique (called transcranial direct current stimulation or tDCS) involves the placement of two sponge electrodes over separate areas of the scalp. tDCS has been shown to be capable of changing the excitability of the superficial neurons immediately

beneath the sponge electrodes. Evidence suggests that anodal stimulation is associated with increased cortical excitability and cathodal stimulation is associated with decreased cortical excitability (Been et al, 2007). The electrodes can therefore be placed on the scalp according to the desired part of the cortex with which to excite.

Across experimental and clinical studies, investigators have demonstrated the analgesic effects that tDCS can have in the experience of pain (see Fregni et al., 2007 for a review). The dorsolateral prefrontal cortex (dlPFC) is one area of the brain that may be particularly relevant in using tDCS to reduce perceived pain and increase pain tolerance. For example, in a study of patients who had undergone ERCP surgery (Borckardt et al., 2011a), there was a significant decrease in reported pain scores and in medication use among the patients who received tDCS. The dlPFC appears to affect emotional aspects of the pain experience and one's perceived controllability of pain (Boggio et al., 2008; Borckardt et al., 2011b), and this may be one way that tDCS affects changes in pain perceptions when anode currents are directed at the dlPFC.

There is also extensive research to support the use of cognitive-behavioral therapy (CBT) in the treatment of pain conditions (e.g., Chen et al., 2004; McCracken & Turk, 2002; Morley et al., 1999). It is well established that CBT is effective in greatly reducing the suffering that patients **with chronic pain endure. There are three main elements to CBT for chronic pain, which include education about how emotions and behaviors can affect one's experience of pain, training in coping strategies to better manage the pain experience (including both behavioral and cognitive strategies), and assistance in the maintenance of those coping strategies (Kerns et al., 2011). Providing accurate information about one's pain experience and training individuals to think about their pain experience in a different way is one relevant aspect of pain treatment that may relate to activity of the prefrontal cortex.**

Despite all of the evidence promoting the use of CBT in treating pain conditions, many individuals still do not benefit from this kind of intervention (Kerns et al., 2011), and it is possible that the use of tDCS over the dlPFC may enhance the potential benefit of cognitive interventions in treating pain. The goal of this study is to investigate how both tDCS and a brief cognitive intervention affect pain tolerance in an experimental setting, and specifically whether the combination of tDCS and a cognitive intervention will enhance pain tolerance. Ultimately, we hope our results will further support the use of tDCS for therapeutic applications in the area of pain management, as well as provide initial evidence of its benefit in combination with cognitive-based treatments for pain that are already in use.

C. PRELIMINARY STUDIES

Provide an account of the principal investigator's preliminary studies pertinent to this protocol and/or any other information that will help to establish the experience and competence of the investigator to pursue the proposed project.

The investigators have conducted multiple studies using tDCS technology that have already demonstrated the benefit of tDCS in increasing pain tolerance and threshold (see Borckardt et al., 2011a, 2011b as examples). The proposed study will be the first to combine tDCS and a cognitive intervention element, although we expect no complications or safety issues with our use of tDCS or cognitive intervention for pain in this study.

D. RESEARCH DESIGN AND METHODS (including data analysis)

Describe the research design and the procedures to be used to accomplish the specific aims of the project. Explain sequentially the study procedure, including all the visits, contacts, and interactions If the study will be designed in phases and each phase will require separate IRB approval, please specifically indicate this in the description. Include how the data will be collected, analyzed, and interpreted and specify what statistical methods will be used. Discuss the particulars of the research instruments, questionnaires and other evaluation instruments in detail. For well known, established valid and reliable test instruments the detail here can be brief. If interviews or groups settings are to be audio taped or video taped describe in detail the conditions under which it will take place. Describe any new methodology and its advantage over existing methodologies. Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims. As part of this section, provide a tentative sequence or time-table for the project. Point out any procedures, situations, or materials that may be hazardous to personnel and the precautions to be exercised.

PARTICIPANTS:

Subjects will be 360 healthy adult volunteers. Subjects will be between the ages of 18 years and 75 years recruited from the greater Charleston area via flyers and newspaper advertisements. Subjects will be paid for their participation.

Laboratory Pain Assessment:

Participants will undergo quantitative sensory testing to measure pain threshold. Ten randomly ordered warming (5) and cooling (5) sequences will be administered with variable (2-10 sec random) lead times and a warm/cool rate of 0.2º C per sec until the subject indicates that a temperature change was perceived. THERMAL PAIN THRESHOLD ASSESSMENT: Cutaneous heat and cold stimuli will be delivered via a Contact Heat-Evoked Potential Stimulator (CHEPS; Medoc, USA) attached to the volar forearm of each subjects left arm. The Method of Limits will be used. The thermode will heat/cool at a rate of 0.5º C per second until the subject indicates that pain was perceived. The procedure will be repeated 10 times (5 hot and 5 cold) and mean values will be used. THERMAL PAIN MAGNITUDE ESTIMATION: Twelve separate 2-second thermal stimuli (4 stimuli each at 46º, 47.5º, 49º C; randomlized) will be applied to each subject's left volar forearm. The target temperature will be sustained for 2 seconds and the thermode will immediately cool to 32º C. After termination of each stimulus, subjects will rate both the intensity and the unpleasantness of the stimulus using the computerized VAS. THERMAL WIND-UP PAIN ESTIMATION: The CHEPS will be used to deliver 20 very brief noxious thermal stimuli to the left volar forearm of subjects at the rate of 1 stimulus (0.75 sec duration) every 1.5 seconds (at 49ºC) thus facilitating C-fiber activation and receptive field expansion of the WDR neurons in the dorsal horn. Subjects will continuously indicate level of pain intensity using a dynamic computerized VAS. MECHANICAL PAIN THRESHOLD ASSESSMENT: The IITC Life Sciences Digital Anesthesiometer will be used to apply pressure to the dorsal surface of the distal phalange of the digiti minimi of the left hand. Pressure will be increased at the rate of 10 grams per second. Participants will stop the stimulus when pressure reaches the pain threshold and the pressure will be recorded in grams.

tDCS:

A single 20-minute tDCS session will be conducted with the Phoresor-II Auto (Model PM850, Iomed, Salt Lake City Utah, USA) using 2.0mA current. Electrodes will be 4x4 cm sponge electrodes soaked in sterile saline. The anode will be placed over the left prefrontal cortex (F3 from the EEG 10-20 system) located via the Beam F3 measurement system. The cathode will be attached to the right shoulder. For sham tDCS, cathode to anode stimulation will be for the duration of the 20-minute session. The current density and total charge delivered by the above parameters is consistent with those used safely in the current research literature on tDCS. Participants will be given vitamin-E cream to apply to the scalp following tDCS to reduce possible skin irritation.

STUDY DESIGN AND PROCEDURES:

Interested participants will call and be pre-screened on the telephone. If interested participants meet the inclusion criteria they will be scheduled for one appointment (lasting approximately 1 hour). Upon coming to the Brain Stimulation Laboratory for the appointment, participants will review and sign the informed consent document. Written informed-consent will be obtained by one of the study investigators or the study coordinator. Participants will complete the Center for Epidemiological Studies 10-item depression scale (CESD), the Beck Anxiety Inventory (BAI), the Reiss-Epstein-Gursky A.S.I., and the Brief Pain Inventory (BPI).

After completing the initial questionnaires they will be taken to the laboratory where they will undergo five trials of the heat tolerance laboratory pain test. The tDCS electrodes will then be placed and fastened with Velcro straps, and the tDCS session will be started. During the tDCS stimulation, participants will undergo the cognitive or educational component of the study as well as pain tolerance assessment procedures every 5 minutes. Patients will randomly receive one of four cognitive behavioral therapy interventions administered through headphones so that the research staff can remain blind. The four cognitive behavioral therapies include Pain-Catastrophizing Cognitive Intervention, Cognitive-Behavioral Distraction Intervention, Cognitively-Mediated Relaxation Intervention, Education-Only Control Condition.

After completion of the tDCS session, participants will again undergo five consecutive trials of the quantitative sensory testing.

At the completion of each appointment participants will be assessed for adverse effects of the stimulation, and they will be asked if they think they received real or fake stimulation and will rate how confident they are in their answer using a 0-10 scale (0= guessing 10= absolutely sure). Participants will also be asked to complete a short supplemental form at the end of the appointment. Participants will also be compensated $40 in cash at that time for their participation in the study.

ANALYSIS:

3 variable MANCOVA will be used to investigate whether change scores (from pre- to post-stimulation) in pain tolerance ratings (i.e., the temperature that participants were no longer able to tolerate the heat stimulus) are significantly affected by stimulation condition. Anodal, Cathodal, and Sham stimulation will be randomly paired with one of the four cognitive behavioral therapies. Both the stimulation and cognitive behavioral therapy will be run through a randomized computer system so as to maintain blinding. A 4X3X2 [CBT group BY tDCS group BY time (pre-post)] mixed multiple analysis of covariance (MANCOVA) will be conducted with the multiple QST values as dependent measures and while controlling for physiological indices across phases (pre- and post-intervention. Gender, age, and race will be controlled in all analyses, although specific demographic variable differences are not expected for the present study. Scores on initial tests (i.e., CESD, BAI, and BPI) may also be examined as control variables

E. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics

- Describe the proposed involvement of human subjects.

- Describe the characteristics of the subject population, including their anticipated number, age range and health status.

Participants will be 360 healthy adult volunteers

Targeted/Planned Enrollment Table

Total Planned Enrollment 360

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	9	8	18
Not Hispanic or Latino	183	159	342
Ethnic Category: Total of All Subjects*	360		
Racial Categories			
American Indian/Alaska Native	10	10	20
Asian	14	11	25
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	65	55	120
White	110	85	195
Racial Categories: Total of All Subjects*	199	161	360

**The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects".*

- Identify the criteria for inclusion or exclusion of any subpopulation.
- Explain the rationale for the involvement of special classes of subjects, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins.
- If you propose to exclude any sex/gender or racial/ethnic group, include a compelling rationale for the proposed exclusion. For example, 1) the research question addressed is relevant to only one gender or 2) evidence from prior research strongly demonstrates no difference between genders.
- Provide either a description of the plans to include children or, if children will be excluded from the proposed research, then you must present an acceptable justification for the exclusion. For example, 1) the condition is rare in children as compared to adults or 2) insufficient data are available in adults to judge risk in children.
- List any collaborating sites where human subjects research will be performed, and describe the role of those sites in performing the proposed research.

N/A

b. Sources of Materials
- Describe the research material obtained from living human subjects in the form of specimens, records, or data.
- Describe any data that will be recorded on the human subjects involved in the project.
- Describe the linkages to subjects, and indicate who will have access to subject identities.
- Provide information about how the specimens, records, or data are collected and whether material or data will be collected specifically for your proposed research project.

We will collect CESD, BAI, BPI and laboratory pain ratings. All of the data will only contain a unique study identifier. The digital file containing identifying information will be kept on the PI locked and secure computer in 518-North, IOP at MUSC. All IRB approved study members will have access to the identifying information.

c. Potential Risks
- Describe the potential risks to subjects (physical, psychological, social, legal, or other), and assess their likelihood and seriousness to the subjects.
- Where appropriate, describe alternative treatments and procedures, including the risks and benefits of the alternative treatments and procedures to participants in the proposed research.

tDCS has been found to be safe in humans with mild procedural side-effects such as tingling sensations under the sponge electrodes (experienced by 70% of tDCS patients), moderate fatigue (35%), and light itching sensations under the sponges (30%). After tDCS, the incidence of side-effects is lower but include headache (12%), nausea (3%) and insomnia (<1%) (Poreisz et al, 2007). If tDCS is delivered at 2mA for 20 minutes per day, every day for 4 or more days in a row, mild skin lesions have been reported. However, these lesions have all been reported to heal without scarring within 1 to 3 weeks following the end of tDCS treatment (Palm et al, 2008). Although there is no evidence to date that tDCS can cause seizures, there is a very minimal risk of seizures associated with tDCS. Qualified nurses and physicians are available 24 hours a day to handle any and all potential complications if they occur. The electrodes and configuration we intend to use in this study are believed to be safer and more comfortable than traditional sponge electrodes. There is also minimal risk of loss of confidentiality.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

- Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.
- Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent.

PI and research assistant will advertise the study via flyers around the MUSC campus. Interested participants will call and be initially screened on the telephone. Participants will be excluded if they have any chronic pain conditions, seizures, a family history of a seizure disorder, are suicidal, have implanted metal devices (e.g., pacemakers, metal plates, wires), are pregnant, have history of brain surgery or history of loss of consciousness >15 minutes, are taking any medication associated with lowered seizure threshold, or are allergic to latex. Written consent to participate will be obtained in a private office in the Brain Stimulation Laboratory at MUSC.

b. Protection against Risk

- Describe planned procedures for protecting against or minimizing potential risks, including risks to confidentiality, and assess their likely effectiveness.
- Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects.
- Studies that involve clinical trials (biomedical and behavioral intervention studies) must include a description of the plan for data and safety monitoring of the research and adverse event reporting to ensure the safety of subjects in Section 4 below.

The study will take place in IOP and qualified nurses and physicians will be available 24 hours a day to handle any and all potential complications if they occur.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

- Discuss the potential benefits of the research to the subjects and others.
- Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.

There are no anticipated direct benefits to participants.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

- Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.
- Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.
- NOTE: Test articles (investigational new drugs, devices, or biologicals) including test articles that will be used for purposes or administered by routes that have not been approved for general use by the Food and Drug Administration (FDA) must be named. State whether the 30-day interval between submission of applicant certification to the FDA and its response has elapsed or has been waived and/or whether use of the test article

has been withheld or restricted by the Food and Drug Administration, and/or the status of requests for an IND or IDE covering the proposed use of the test article in the research plan.

Chronic pain is a huge public health concern and more treatment options are needed. It is believed that the information gained through this investigation might help us determine the feasibility of tDCS in combination with cognitive interventions as a treatment option for certain types of pain.

5. SUBJECT SAFETY AND MINIMIZING RISKS (Data and Safety Monitoring Plan)

*Studies that involve *clinical trials (see description below) must include a description of the plan for subject safety and minimizing risks of the research, including data monitoring and adverse event reporting to ensure the safety of subjects. The complexity of the plan should be determined by the level of risk to subjects. The plan should specify: 1) what will be monitored, 2) how frequently the monitoring will occur, 3) who will be responsible for the monitoring, and 4) study endpoints.*

Participants will be carefully monitored for the entirety of the study. Any adverse events will be recorded and reviewed by the PI. Applicable cases will be reported to the IRB according to the IRB policy. This data will also be used to further establish the safety profile of tDCS in the current research literature.

*Clinical Trials
A clinical trial *is a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).*
Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective. Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits these criteria of a clinical trial. Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision-making for the subject or the test itself imposes more than minimal risk for subjects.

F. REFERENCES/LITERATURE CITATIONS

List all references. Each reference must include the title, names of all authors, book or journal, volume number, page numbers, and year of publication. The reference should be limited to relevant and current literature. It is important to be concise and to select only those literature references pertinent to the proposed research.

Been, G., Ngo, T. T., Miller, S. M., & Fitzgerald, P. B. (2007). The use of tDCS and CVS as methods of non-invasive brain stimulation. *Brain Research Reviews, 56*, 346-361.

Boggio, P. S., Zaghi, S., Lopes, M., & Fregni, F. (2008). Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. *European Journal of Neurology, 15,* 1124-1130.

Borckardt, J. J., Romagnuolo, J., Reeves, S., et al. (2011a). Feasibility, safety, and effectiveness of transcranial direct current stimulation for decreasing post-ERCP pain: A randomized, sham-controlled, pilot study. *Gastrointestinal endoscopy, 73,* 1158-1164.

Borckardt, J. J., Reeves, S. T., Frohman, H., et al. (2011b). Fast left prefrontal rTMS acutely suppresses analgesic effects of perceived controllability on the emotional component of pain experience. *Pain, 152,* 182-187.

Chen, E., Cole, S. W., & Kato, P. M. (2004). A review of empirically supported psychosocial interventions for pain and adherence outcomes in sickle cell disease. *J Pediatr Psychol, 29,* 197-209.

Fregni, F., Freedman, S., & Pascual-Leone, A. (2007). Recent advances in the treatment of chronic pain with noninvasive brain stimulation techniques. *Lancet Neurol, 6,* 188-191.

Kerns, R. D., Sellinger, J., & Goodin, B. (2011). Psychological treatment of chronic pain. *Annual Review of Clinical Psychology, 7,* 411-434.

McCracken, L. M., & Turk, D. C. (2002) Behavioral and cognitive–behavioral treatment for chronic pain: outcome, predictors of outcome, and treatment process. *Spine, 27,* 2564-2573.

Morley, S., Eccleston, C., & Williams, A. (1999). Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain, 80,* 1-13.

Palm, U., Keeser, D., Schiller, C., et al. (2008). Skin lesions after treatment with transcranial direct current stimulation (tDCS). *Brain Stimulation, 1,* 386-387.

Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Research Bulletin, 72,* 208-214.

G. CONSULTANTS

Where applicable, attach electronic versions of appropriate letters from all individuals confirming their roles in the project. Go to the application under "additional uploads" to attach this information.

H. FACILITES AVAILABLE

Describe the facilities available for this project including laboratories, clinical resources, etc.

The Brain Stimulation Laboratory has all equipment, personnel and resources necessary to conduct the proposed pilot study.

I. INVESTIGATOR BROCHURE

If applicable, attach the electronic version of the investigator brochure. Go to the application under "additional uploads" to attach this information.

J. APPENDIX

Attach any additional information pertinent to the application, such as surveys or questionnaires, diaries or logs, etc. Go to the application under "additional uploads" to attach this information.