

**Medical University of South Carolina  
Protocol**

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**Study Title: Effect of Cognitive Behavioral Therapy and Transcranial Direct Current Stimulation (tDCS) on Fibromyalgia Patients.**

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**A. SPECIFIC AIMS**

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**Aim:** Determine the effects of CBT, anodal tDCS over left DLPFC, and combined CBT+tDCS on clinical pain and functioning among a sample of patients with fibromyalgia

*Hypothesis 1a: CBT alone will be associated with significant improvements in pain and functioning*

*Hypothesis 1b: Anodal tDCS plus CBT will yield significant improvements in pain and functioning that exceed those of CBT alone.*

This study will be the first randomized, double-blind, controlled study of tDCS technology as an adjunctive pain management strategy for fibromyalgia pain. Data from this trial will likely yield information regarding the feasibility and efficacy of tDCS+CBT as a chronic pain-management approach.

**B. BACKGROUND AND SIGNIFICANCE**

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**FIBROMYALGIA (FM):** Fibromyalgia is considered to be a multifactorial disorder resulting from the interaction of both genetic and environmental factors, which contribute to its occurrence and expression<sup>3</sup>. Symptoms of Fibromyalgia include widespread muscle pain, fatigue, disruption in sleep patterns, loss of memory, and mood disorders. Fibromyalgia is commonly associated with other medical conditions such as depression, rheumatoid arthritis, and other stress-related disorders such as posttraumatic stress disorder. The cause of fibromyalgia is unknown; the most prevalent theory being that those suffering from the disease have a lower threshold for pain due to an increased reactivity of pain sensitive nerve cells. The pain and physical debility of this disease produce changes in nearly every area of life. The prevailing medical treatments are aimed at suppression of symptoms, analgesia, and prevention of damage to joints, but these treatments can have adverse side-effects. Therefore, several non-pharmacological pain management techniques have emerged<sup>2-8</sup>.

**PAIN AND THE BRAIN:** Pain is a complex experience that has sensory-discriminatory, motivational-affective and cognitive-evaluative dimensions<sup>6</sup>. Experimental and clinical fMRI findings suggest that parietal areas, including the primary somatosensory cortex, are mainly involved in the sensory-discriminative dimension of pain experience and frontolimbic networks and the anterior cingulate cortex (ACC) are involved in the affective dimension<sup>7 8, 9 7, 10 11-13 14, 15 16</sup> The role of the left prefrontal cortex in

(PFC) pain control is unclear however, there is evidence to support the concept that left PFC activation is negatively correlated with pain unpleasantness<sup>17</sup> suggesting a possible governing role of the PFC on the affective dimension of pain experience<sup>18</sup>. Recent studies of expectancy and cognitively-mediated analgesia seem to suggest that cognitive effects on pain perception may involve genuine analgesia mediated by  $\mu$ -opioid systems<sup>19, 20</sup> that is associated with decreased activation of the thalamus, insula and ACC. These effects correlate with prefrontal cortex activation<sup>21</sup>. Thus, prefrontal activation/stimulation might result in analgesic effects, presumably by modulating limbic response to pain.<sup>22 23 24</sup>

**MINIMALLY INVASIVE BRAIN STIMULATION AND PAIN:** There is some evidence that electrical stimulation of the motor cortex can ameliorate pain<sup>25-28</sup>. The PFC is another studied target for pain relief, and may be specifically helpful in reducing the affective dimension of pain. Stimulation of the PFC increases thermal pain thresholds in healthy adults<sup>24</sup> and reduces neuropathic<sup>29</sup> and fibromyalgia pain<sup>23 30</sup>. tDCS involves the application of low-amplitude electric current to the brain. A battery-powered current generator is attached to two sponge electrodes soaked in saline and held in place by a non-conducting montage. Sufficient current penetrates the brain and modifies transmembrane neuronal potential<sup>31, 32 33</sup> influencing excitability and modulating the firing rate of neurons. Anodal tDCS applied over the human cortex increases excitability, while cathodal tDCS applied over the same area decreases it<sup>34 35 36, 37 38</sup>. While tDCS appears to have direct effects on brain activity, structure, and neuronal organization, the effects are likely mediated by several factors, the most important of which may be the activity of the brain during stimulation. It appears that tDCS may be a brain stimulation tool that can be used to facilitate or inhibit endogenous cortical and subcortical processes, but not necessarily directly or independently engender large, directly observable behavioral changes unless strategically combined with specific brain activity patterns. This notion has already been embraced in the area of stroke rehabilitation wherein tDCS is combined with rehab therapy to produce significantly enhanced recovery effects.<sup>39</sup>

### **COGNITIVE AND BEHAVIORAL ASPECTS OF PAIN PERCEPTION:**

Cognitive Behavioral Therapy (CBT) for Pain: CBT is emerging as an important adjunct to medical treatment for FM. CBT for FM is typically aimed at improving pain coping skills and targeting behaviors associated with exacerbation of fatigue and physical disability. The conceptualization of pain as having both cognitive and emotional components paved the way to the assumption that changing a patient's thoughts and attitudes may alter his/her subjective experience of pain. To date several promising controlled investigations of cognitive behavioral therapy (CBT) for FM have been conducted<sup>1-3 4</sup>. The CBT packages that were applied in these studies generally consisted of the following standard procedures: relaxation training, cognitive pain coping strategies, and self-management strategies. Overall, these studies provide good evidence for the effectiveness of brief CBT in FM compared to an attention placebo, patient education, symptom monitoring and/or no treatment control conditions. CBT for chronic pain is associated with increased activation in the ventrolateral prefrontal/lateral orbitofrontal cortex<sup>40</sup> and may activate a cortical control mechanism over pain experience. Given the ability of tDCS to enhance cortical excitability in targeted brain areas, it is possible that combining CBT with prefrontal tDCS could enhance the overall effect and possibly its duration.

Pain Catastrophizing or cognitive characterizations of pain as awful, horrible and unbearable, is increasingly being recognized as an important factor in the experience of pain.<sup>41 42-46</sup> Catastrophizing appears to augment pain by enhancing attention to painful stimuli, and heightening emotional responses.<sup>47</sup> Catastrophizing is associated with increased activity in the ipsilateral claustrum, cerebellum, DLPFC, parietal cortex, dorsal ACC, medial frontal cortex, and lentiform nuclei<sup>47</sup> suggesting that pain catastrophizing is significantly associated with increased activity in brain areas related to anticipation of pain, attention to pain, and emotional aspects of pain.

Pain and Cognitive-Behavioral Distraction: Emotional and attentional states appear to contribute to the multidimensional pain experience<sup>48</sup>, and pain can be therapeutically reduced by cognitive manipulation and distraction tasks.<sup>49-52</sup> The DLPFC appears to exert active control on pain by modulating cortico-subcortical and cortico-cortical pathways<sup>17</sup> and distraction significantly increases activation of the

cingulo-frontal cortex including the orbitofrontal and perigenual ACC, as well as the PAG and the posterior thalamus.<sup>53</sup> These findings suggest that the cingulo-frontal cortex may exert top-down influences to gate pain during distraction.

Pain and Autonomic Regulation: Relaxation-training aimed at decreasing physiological arousal is a standard component of CBT for pain.<sup>54</sup> Several neuroimaging studies suggest that during relaxation, brain areas including ACC and insula provide a link between cognitive behavior and autonomic bodily responses.<sup>55-58</sup> Activity in these areas can have modulatory effects on autoregulatory processes<sup>58-60</sup>

Pain and Perceived Control: There is now convincing evidence that acute and chronic pain are perceived as less intense when they are or appear to be controllable<sup>61 62 63 64</sup>. Further, perceived control has been shown to attenuate cortical and subcortical responses to pain.<sup>65 66-68</sup> Perceived control over pain is associated with activation in dorsal ACC, right dorsolateral, and bilateral anterolateral PFC and activation in ACC and PFC is negatively correlated with pain intensity ratings.<sup>61, 65</sup> It may be that prefrontal activation via CBT and/or tDCS in chronic pain patients could provide a reinforced cortical governance signal to limbic regions.<sup>69</sup> This might result in reduced pain behaviors, symptoms, longer-term benefit & improved coping.

### **C. PRELIMINARY STUDIES**

TMS and Fibromyalgia: To date there have been three published studies involving rTMS and fibromyalgia<sup>63, 95, 96</sup> and one additional pilot trial conducted by the Investigators (described in the Innovation section). Sampson<sup>63</sup> examined the effect of slow-frequency (1 Hz) rTMS in subjects with treatment-resistant depression and borderline personality disorder (BPD). A convenience sample of 4 subjects in this study also had a previous diagnosis of fibromyalgia and she reports on the effects of TMS on fibromyalgia pain in this sample. The design was sham-controlled, with blinded patients and raters, but the treater, standing next to the patient, knew the randomization status. rTMS was produced using a Magstim Super Rapid repetitive stimulator and a 70-mm figure-of-eight coil. 1-hertz rTMS was applied 5 cm anterior to the optimal motor cortex stimulation site to approximate localization of the R-DLPFC. rTMS was applied using a frequency of 1 Hz, intensity of 110% motor threshold (MT), and two 800 second trains with an intertrain interval of 60 seconds, for a total of 1,600 stimuli per session. One of the four FM subjects received 10 sham rTMS treatments using a 90-degree coil rotation before receiving active rTMS. Subjects received active rTMS over 4 weeks, and one subject received an additional 12 treatments over 6 weeks as part of a taper protocol for those who had remission of depression (> 50% decline and <10 on the Hamilton Rating Scale for Depression (HRSD)). Although improvement on HRSD and ratings were statistically significant, only one subject had a remission of depression. However, all subjects noted an improvement in fibromyalgia pain, with two subjects reporting complete resolution of pain. One subject received sham rTMS for 2 weeks with no pain improvement during that time. One subject noted improvement in pain during the first week of treatment, and two noted improvement during week 3 of treatment. Two subjects provided pain ratings during treatment and two described changes in pain retrospectively when contacted after it was noted that rTMS might be altering pain. The subjects were contacted repeatedly after finishing the acute series of treatment to assess the recurrence of pain. The subjects were defined as having recurrence of pain when reported ratings increased by at least 1.5 points. The duration of pain improvement ranged from 15 to 27 weeks. Given the limited reduction in depression ratings, the reduction in fibromyalgia pain likely cannot be completely explained by the treatment of depression alone. Notably, the subjects' pain improvement was sustained for a number of weeks after rTMS, which softly suggests the possibility that rTMS applied to the DLPFC may be clinically useful in reducing fibromyalgia pain. This study was not prospectively designed nor powered to assess changes in fibromyalgia pain and involved only 4 subjects, all with significant depression co-morbidity. Half the subject data was retrospectively gathered. Furthermore the sham system was not able to keep the treater blind. Nonetheless this study suggests that prefrontal cortical rTMS may help reduce fibromyalgia pain.

Carretero et al<sup>96</sup> recently attempted to replicate the Sampson findings using similar parameters but in a larger sample with randomization and a single-blind sham controlled arm. 14 subjects underwent real TMS and 12 received sham. The real rTMS was employed with DANTEC TMS equipment at the R-DLPFC location. Subjects received 1 Hz TMS for 60 seconds on and 45 seconds off at 110% MT for approximately 30 minutes for a total of 1200 pulses per session. Subjects received 20 daily sessions in total. Both groups improved in fatigue and CGI but there was no improvement in pain and depression. Furthermore there was no significant difference between real and sham TMS in this sample. However, the sham system was suboptimal with simply a shift in the TMS coil to 45 degrees so that sound is heard but no cutaneous sensation was experienced. More importantly subjects received 400 fewer pulses per session for a total of 8000 fewer pulses than the Sampson group. Thus subjects may have been relatively “underdosed” in comparison, but they failed to replicate the TMS FM treatment effect with right-sided, prefrontal, slow-TMS treatment.

Passard et al<sup>95</sup>, hypothesized that rTMS of the motor cortex might reduce chronic widespread pain in patients with fibromyalgia. They employed a randomized, double blind, sham-controlled parallel group study analyzing the analgesic effects of repeated daily sessions of unilateral rTMS in 30 patients with widespread pain, quality of life, mood, and anxiety problems due to fibromyalgia. Tender point pain threshold was a secondary outcome. Each treatment session employed a stimulation frequency of 10 Hz and 80% resting motor threshold intensity, resulting in a total of 2000 pulses per session. The primary outcome measure was self-reported average pain intensity over the prior 24 hours using an 11-point numerical scale. Average pain intensity was reported for 1 week as a baseline, during treatment (days 1-14) and until the first follow-up visit to make it possible to determine the onset of treatment effects, then was assessed at each follow-up visit on days 15, 30, and 60. Four patients (two per treatment group) withdrew from the trial between days 30 and 60. Pain intensity was similar in the two groups at baseline and rTMS had a significant effect on average pain intensity scores between baseline and day-15 in comparison with sham stimulation. This effect was not maintained on days 30 and 60. Average pain intensity was significantly lower in the active rTMS group than in the sham stimulation from day 5 to day 14. On day 15, McGill Pain Questionnaire total score and the sensory and affective subscores were significantly lower in the active rTMS group than in the sham-stimulation group. The difference in affective subscore persisted until day 30, whereas the sensory subscore did not. Subjective global pain relief over the last week was significantly greater in the active than in the sham-stimulation group up to day 30. Mean depression and anxiety scores were similar in the two treatment groups at baseline and were not significantly changed by active or sham stimulation. rTMS had no significant effect on the number of tender points. This study showed that rTMS of the primary motor cortex induced a long-lasting decrease in pain and improved quality of life in patients with fibromyalgia, without affecting mood or anxiety levels. One limitation of this study is the design of the sham system.

Table 1. Overview of current TMS fibromyalgia literature including the pilot study recently completed by the Investigators (Short et al)

Study	Sample Size	Cortical Target	Frequency	Intensity	Pulses Per Session	Sham System	Blind	Concurrent Meds
Sampson et al	4	Right Dorsolateral Prefrontal Cortex	1 Hz	110% rMT	1600	Did not control for Scalp Sensations	Treater was not blind	Permitted
Carretero et al	26	Right Dorsolateral Prefrontal Cortex	1 Hz	110% rMT	1200	Did not control for Scalp Sensations	Single-Blind	Permitted
Passard et al	30	Motor Cortex	10 Hz	80% rMT	2000	Did not control for Scalp Sensations	Double-Blind	Permitted
Short et al	20	Left Dorsolateral Prefrontal Cortex	10 Hz	120% rMT	4000	Controlled for Scalp Sensations	Single-Blind	Permitted

Per description, it makes similar sounds as active rTMS, however there is no form of superficial stimulation to the scalp, which can be problematic as otherwise the active and sham treatments are easily discerned.

There is evidence in the TMS-literature to suggest that slow (1 Hz) right prefrontal TMS has anti-depressant effects as does fast (10 Hz) left prefrontal TMS, however fast left prefrontal TMS appears to have larger effects that benefit more patients with depression than slow right. Following from these findings as well as several pilot studies conducted by our group showing analgesic benefits of fast left TMS in laboratory pain models<sup>97</sup>, chronic neuropathic pain<sup>98</sup>, and post-surgical pain<sup>99-101</sup>, we recently completed a preliminary single-blind, sham-controlled trial of fast left dorsolateral prefrontal

rTMS among a cohort of 20 patients with fibromyalgia. Findings suggest significant, long-lasting benefits of real rTMS compared to sham on FIQ scores, average daily pain, and tender points (see Innovation section for a full description of this pilot study).

Noninvasive brain stimulation is in its infancy, particularly its application in the management of chronic pain disorders such as fibromyalgia. Techniques such as TMS and tDCS have shown some preliminary promise in the management of FMS, but more work is needed in this area. All the previous studies to date suffer some significant limitations that prohibit inferences regarding TMS efficacy for FMS pain. In all previous trials, patients were permitted to be on concomitant pain medications muddying the available TMS-efficacy inferences. The sham technologies employed in most previous trials did not permit for control over effects of scalp discomfort and other procedural pain associated with real TMS (not present during sham stimulation). Most trials to date have been single-blind, or have used methodologies that permit the interaction between patients and un-blinded investigators. The TMS cortical targets, frequencies, total pulses and intensities studied have varied considerably from study to study as have the methods for cortical localization. The typical outcome measures employed have been solely self-report and no objective measures of activity levels or sleep have been used, nor have experience sampling technologies been employed to capture unbiased daily pain ratings. Lastly, the sample-sizes employed in previous studies have been small and in some cases were convenience samples. *While the available preliminary data suggest the presence of a TMS effect on FMS pain, a more definitive, well-controlled investigation is needed to establish TMS as an efficacious, viable treatment option for patients with FMS.*

**TDCS AND PERCEIVED PAIN CONTROL:** Participants were 41 healthy individuals aged 20-57. A single 20-minute tDCS session was conducted using 2.0mA current during the same perceived controllability paradigm described above.<sup>65</sup> One electrode was applied to the left DLPFC and the other electrode was placed on the subject's right arm. Subjects received either anodal or cathodal PFC stimulation (randomized). Thermal stimulation delivered during perceived-control trials compared to no-perceived-control was rated less painful (by 2.75 points) across groups. Unpleasantness VAS ratings were significantly lower for participants randomized to the anode group (mean=56.49; SEM=4.26) compared to those randomized to the cathode tDCS group ((mean=69.39; SEM=3.83);  $t(39)=2.25$ ,  $p=0.03$ ) suggesting that anodal stimulation enhanced the analgesic benefits of perceived controllability and/or that cathodal stimulation of the left DLPFC disrupted those analgesic benefits. Participants randomized to the anode group rated their perceived control over the thermal pain stimuli at 4.7 out of 10 (SEM=0.49), whereas those randomized to the cathode tDCS group rated their perceived control lower at 3.24 (SEM=0.56;  $t(39) = -1.95$ ,  $p=.05$ ). These findings suggest that anodal tDCS of the DLPFC may enhance the analgesic effects of perceived-control and enhance the subjective sense of control.

**COMBINED CBT and tDCS INTERVENTION EFFECTS ON PAIN PERCEPTION:** To directly address the aims of the present proposal, in a recent preliminary pilot, the Investigators examined the effects of anodal versus cathodal tDCS over the left DLPFC in combination with a laboratory CBT intervention on thermal pain tolerance in 8 healthy volunteers. Participants underwent repeated heat tolerance testing using the Medoc Pathway system before, during and after the combined tDCS+CBT intervention. Participants were randomly assigned to receive anodal or cathodal tDCS delivered over the left DLPFC. For this preliminary pilot, participants all listened to a recording of a laboratory-version of a CBT intervention that focused on 3 distinct elements: 1) identification of catastrophizing language and replacement with more realistic and attenuated linguistic tags for thermal experiences. 2) identification and challenging of automatic negative self-effacing thoughts related to the tolerance task, and 3) a behavioral distraction strategy. Anodal tDCS applied to the left DLPFC during the CBT intervention was associated with a significant increase in thermal pain tolerance whereas cathodal stimulation appears to have blunted the analgesic benefit of the CBT intervention. Despite all subjects receiving the same CBT intervention, those that received simultaneous anodal stimulation of the left DLPFC found the CBT intervention significantly more helpful ( $p<.05$ ) and found the strategies presented more useful in improving pain tolerance ( $p<.05$ ) than those who received cathodal stimulation. These findings support the notion that engaging cognitive neural circuits that have been shown to play a role in the

down-regulation of pain experience and then exciting the circuits with tDCS might offer synergistic benefit.

#### **D. RESEARCH DESIGN AND METHODS (including data analysis)**

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**OVERVIEW:** Pilot clinical trial-- Patients with FM will receive a brief course (6 sessions) of manualized CBT for pain (or education-only control) combined with anodal or sham tDCS over the left DLPFC

**PARTICIPANTS:** Participants will be 72 patients meeting the American College of Rheumatology (ACR) criteria from diagnosis of fibromyalgia for at least 1-year. Patients must not have any chronic pain conditions other than fibromyalgia, and must not be on chronic opioid therapy for pain. Patients with a history of seizures, who are or might be pregnant, or with metal/electronic implants or devices above the waist will be excluded to ensure tDCS safety. Patients with moderate to severe depression (HRDS>18) at the time of randomization will be excluded, however patients with no depression or only mild depression (HDRS<19) will be eligible provided that the onset of the first depressive episode was after the onset of fibromyalgia (as is commonly seen in patients with chronic pain) in order to exclude patients for whom chronic widespread pain might be a somatic manifestation of the depressive illness. To be eligible for enrollment, BAI scores must be <16 to limit the sample to patients with minimal to no clinical anxiety problems.

**tDCS METHODS:** tDCS will be delivered in 30-minute-sessions and will be conducted with the Phoresor-II Auto (Model PM850) using 2mA current. This constant current device ramps up to the desired amplitude to minimize discomfort for participants and ramps the amplitude back to 0mA at the end of the session. Electrodes will be standard small (4cm X 4cm) sponge electrodes soaked in a sterile solution of 0.9% sodium chloride insulated by a latex casing. The current density and total charge delivered by the above parameters is consistent with those used safely in the current research literature on tDCS. In all tDCS conditions, participants will undergo anodal stimulation of the left DLPFC (Brodmann Area 9; BA9) and cathodal stimulation of the right DLPFC (which is consistent with the majority of published prefrontal tDCS studies for pain to date) during each of the 6 CBT sessions. The electrodes will be fastened with Velcro strap(s). Specially designed software (by the Investigator) interfaces with an ONTRAK ADU218 Solid State Relay I/O interface connected to the tDCS device permitting normal and reverse current flow between the electrodes in a manner that is completely masked. The software reads the assigned condition directly from an encrypted subject-randomization-file and delivers anodal, cathodal or sham stimulation in a blinded fashion.

**Clinical Pilot Trial:** The proposed clinical pilot will investigate the effects of prefrontal tDCS combined with a standard manualized CBT intervention for chronic pain.<sup>70</sup> One session will be conducted each week for 6 weeks, and the double-blind tDCS delivery system will be used to ensure that tDCS randomization remains completely masked throughout the trial.

**Cognitive-Behavioral Therapy Intervention:** A 6-session version of the Otis standardized CBT manual for chronic pain will be used. Each session will last 60-minutes and standard CBT homework assignments will be employed as per the manual. A specially-trained pain-psychologist will implement the manualized CBT.

**QUANTITATIVE SENSORY TESTING (QST):** For female participants, all QST will be conducted during the luteal phase of the menstrual cycle. For patients in the clinical pilot, repeated QST sessions will be conducted at the same time of day. Participants will not be permitted to take any prn analgesic medication on the day of the QST session(s) prior to assessment. THERMAL PAIN THRESHOLD ASSESSMENT: Cutaneous heat stimuli will be delivered via a the ATS thermode of the Medoc Pathway System attached to the volar forearm of each subjects left arm. The Method of Limits will be

used. The thermode will heat at a rate of 0.5° C per second until the subject indicates that pain was perceived. The procedure will be repeated 5 times and mean values will be used. THERMAL WIND-UP PAIN ESTIMATION: The ATS thermode 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 49°C) 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. A FM trigger point evaluation will be conducted using an analog dolorimeter.

#### Dependent Measures:

THE BECK DEPRESSION INVENTORY (BDI) is a well-researched, brief self-report depression-screening instrument. This instrument will be used for screening purposes in the laboratory study and to characterize depression in the clinical cohort. The BDI scale assesses suicidal ideation, those patients exhibiting suicidal ideations will be referenced to a therapist in order to further manage their depressive symptoms.

THE BECK ANXIETY INVENTORY (BAI) is a well-researched, brief self-report anxiety-screening instrument. It assesses different aspects of anxiety experience (e.g., physiological, cognitive, behavioral).

THE BRIEF PAIN INVENTORY (BPI) is a self-report questionnaire designed to assess pain intensity and the impact of pain on general functioning, relationships and mood.

DAILY PAIN/MOOD DIARIES will be administered via paper and pencil to patients in the clinical pilot Diaries will assess daily (via VAS) average pain, pain at its worst, pain unpleasantness, mood, activity level, and will capture hours of sleep and sleep quality ratings.

THE MCGILL PAIN QUESTIONNAIRE (MPQ) is a self-report scale designed to capture the quality and intensity of pain experience. The ratings load onto 4 factors: 1) Sensory, 2) Affective, 3) Evaluative, and 4) Miscellaneous.

THE MOS SHORT-FORM12 HEALTH SURVERY (SF12) will be used to assess quality of life across the eight QOL domains captured with the measure during the trial.

THE FIBROMYALGIA IMPACT QUESTIONNAIRE will be used to assess pain symptoms and functioning specific to FM.

#### PROCEDURES:

**Clinical Pilot Trial:** Patients will be recruited by fliers or referred by providers in the Chronic Pain Clinic, Dept. of Rheumatology and the Behavioral Medicine Clinic at MUSC. Participants will be screened on the telephone, consented, oriented to the study, and instructed in the use of pain diaries. After a 2-week baseline phase, patients will undergo QST. They will then start the manualized CBT intervention in the Behavioral Medicine Clinic at MUSC with simultaneous tDCS (real or sham; randomized and masked). Participants will undergo 1 session per week for 6 weeks. After the last session, participants will undergo another QST session. Patients will continue to complete the pain diaries throughout the treatment as well as a 4-week follow-up phase. At 3 and 6 months, participants will return to the lab to re-complete the dependent measure battery.

**DATA ANALYSIS PLAN AND POWER:** Hierarchical Linear Modeling (HLM) will be used to examine changes in pain, sleep and activity over time while controlling for mood (time-series), and controlling for

baseline depression, anxiety and pain scores as a function of group (active vs sham tDCS). HLM will also be used to examine changes in quality of life and functional impairment due to pain. Previous research on the effects of CBT for pain and of tDCS for pain suggests that each is associated with a medium effect-size. To be conservative, assuming that there is no synergistic interaction-effect of combined tDCS and CBT, power is good to detect a group-level main effect ( $1-\beta > .80$ ) with as few as 18 subjects per group. If the interaction-effect is large, as is expected, power is excellent to detect main and interaction effects ( $1-\beta > .90$ ).

## **E. PROTECTION OF HUMAN SUBJECTS**

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### 1. RISKS TO THE SUBJECTS

The sample will be 72 patients with chronic pain due to FM (BPI pain on average score  $>4/10$ ) between the ages of 21 and 85, with a duration of illness of at least 1 yr and the diagnosis of FM. Interested participants will review and sign the informed consent document with one of the study investigators. Participants will be excluded if they have uncontrolled epilepsy, metal implants in the head or known brain tumors or lesions that intersect the area of stimulation, and severe latex allergies. If a participant indicates the possibility of pregnancy, a urine pregnancy test will be administered. Participants will be excluded from the study if they screen positive for pregnancy. Participants will also be screened for a history of closed head injury with loss of consciousness lasting more than 5 minutes, a history of seizures, a family history of seizures, metal implants above the waist, eczema or other sensitive skin conditions, and current medication usage. These screening measures will be used to assess the risk to benefit ratio for inclusion in the study on a case-by-case basis. If participants indicate on the BDI intent to harm themselves, they will be evaluated by a study psychologist. Pending results of the evaluation, participants will be admitted or hospitalized for appropriate care as necessary. There is no safety data to suggest increased risk for the older population, age 75-85, in this study. There is a possibility of increased skin irritation in this older population.

### **Targeted/Planned Enrollment Table**

Total Planned Enrollment 72

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	2	1	3
Not Hispanic or Latino	42	27	69
<b>Ethnic Category: Total of All Subjects*</b>	72		
Racial Categories			
American Indian/Alaska Native	1	1	2
Asian	2	1	3
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	19	9	28
White	22	15	37
<b>Racial Categories: Total of All Subjects*</b>	45	27	72



#### b. Sources of Materials

We will collect patient-reported depression, anxiety, sleep, activity, pain scores, and QST scores. All of the data will only contain a unique study identifier. The digital file containing identifying information will be kept on the PI's locked and secure computer. Only the PI and primary research assistant will have access to the identifying information.

#### c. Potential Risks

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). All patients will be inpatient at MUSC and under the care of a licensed physician. Qualified nurses and physicians are available 24 hours a day to handle any and all potential complications if they occur.

The current-density of the proposed treatment is 0.125mA/cm<sup>2</sup> which is substantially less than the current density required to induce brain tissue damage (25mA/cm<sup>2</sup>). Further, the current (2mA) is over 400 times less than the average current used to induce seizures in electro-convulsive therapy (800mA). While this treatment is indeed investigational and the potential long-term effects are largely unknown, the parameters we plan to use appear to be extremely safe and are within the range used in the published tDCS-pain literature. The risks associated with the use of topical creams (benzocaine and vitamin-E/Aloe) are minimal but include skin irritation and contact dermatitis. If these occur, the investigators will immediately remove any cream from the subject's skin and apply a wet compress.

In a very recent study of tDCS effects on post-operative TKA pain, there were no adverse events associated with tDCS. The most common side effects reported by participants were mild tingling and itching under the electrodes. The benefits of this study appear to outweigh the risks as the slopes of the cumulative PCA usage curves were significantly different between the real and sham tDCS groups; those TKA in the real tDCS group used 44% less PCA dilaudid at 48-hours post-op than did the sham tDCS group. Despite significantly lower PCA dilaudid levels, VAS ratings of pain-on-average were also significantly lower in the real tDCS group ( $t(37)=2.28, p=.029$ ).

## 2. ADEQUACY OF PROTECTION AGAINST RISKS

#### a. Recruitment and Informed Consent

Participants will be excluded if they have uncontrolled epilepsy, metal implants in the head or known brain tumors or lesions that intersect the area of stimulation, and severe latex allergies. If a participant indicates the possibility of pregnancy, a urine pregnancy test will be administered. Participants will be excluded from the study if they screen positive for pregnancy. Participants will also be screened for a history of closed head injury with loss of consciousness lasting more than 5 minutes, a history of seizures, a family history of seizures, metal implants above the waist, eczema or other sensitive skin conditions, and current medication usage. These screening measures will be used to assess the risk to benefit ratio for inclusion in the study on a case-by-case basis. If participants indicate on the BDI intent to harm themselves, they will be evaluated by a psychiatrist or psychologist from the Institute of Psychiatry. Pending results of the evaluation, participants will be admitted or hospitalized for appropriate care as necessary. There is no safety data to suggest increased risk for the older population, age 75-85, in this study. There is a possibility of increased skin irritation in this older population.

#### b. Protection against Risk

There is a risk of a loss of confidentiality of your personal information as a result of participation in this study. Qualified nurses and physicians are 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

All participants might receive benefit from the CBT intervention. Participants receiving real tDCS+CBT may experience less chronic pain resulting from their fibromyalgia than they would have without the tDCS treatment. Previous investigations suggest that those patients receiving real tDCS and a cognitive behavioral therapy treatment may receive an increased analgesic effect in the treatment of their chronic pain.

### 4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Pain is a huge public health concern and the proper management of pain is a high national healthcare priority. New treatments are needed for the management of pain, and minimally-invasive brain stimulation techniques appear to be well-suited for the management of certain types of pain. Currently, tDCS is an investigational treatment and is not approved by the FDA as a treatment for pain. The available evidence to date suggests that tDCS is safe in humans with minimal negative side-effects.

This study will be the first randomized, double-blind, controlled study of tDCS technology in combination with cognitive behavioral therapy as an adjunctive pain management strategy for fibromyalgia patients. Data from this trial will likely yield information regarding the feasibility and efficacy of tDCS as a chronic pain management approach. If the proposed pilot trial suggests significant and meaningful effects of tDCS in combination with CBT as an adjunctive pain management strategy, this might change the way pain management is approached in the future. Findings from this study will be used to evaluate the necessity for an even larger-scale, multi-site clinical trial of the technique, and to determine whether future investigations of tDCS and CBT are merited.

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

All adverse events regardless of their perceived relationship to the investigational treatment will be recorded and reported to the MUSC IRB. This data will also be used to further establish the safety profile of tDCS in the current research literature.

## **F. REFERENCES/LITERATURE CITATIONS**

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*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.*

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#### H. FACILITIES AVAILABLE

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

The PI (an independent investigator in the Brain Stimulation Laboratory) possesses the tDCS machine described in this protocol. All participants will be involved in a standard clinical protocol at MUSC and will have all of the resources available to them and to manage their chronic pain. The Behavioral Medicine clinic is a large, active clinic staffed with nurses, pharmacists, psychiatrists and psychologists and specializes in the behavioral management of chronic pain.