Medical University of South Carolina
Protocol

Title: The Effects of Cognitive Behavioral Therapy and Transcranial Current Stimulation (tDCS) on Chronic Lower Back Pain

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SPECIFIC AIMS

As a result of sustained operations in Afghanistan and Iraq, an increasing number of U.S. military personnel and Veterans are in need of effective pain management treatment. Chronic low back pain (CLBP) is the most common pain condition among returning Veterans, and is associated with high levels of opioid analgesic prescribing in VA clinics, and multiple co-morbid problems including depression, anxiety, opioid misuse, and sleep disturbance. Although opioids are effective for acute pain, they are not very effective as a long-term treatment strategy. Furthermore, opioids are associated with significantly increased risk of misuse, addiction, diversion, overdose and death. Consequently, there is a critical need for the development of alternative, effective treatments for CLBP that can be implemented in VA-based healthcare settings.

Although cognitive behavioral therapy (CBT) is the most widely used, evidence-based, non-pharmacologic treatment for sleep and pain, its effects on pain are modest when used in isolation. Enhancing the effectiveness and durability of CBT is critical to providing a viable non-pharmacologic treatment option to the millions of Veterans suffering from chronic pain and reducing their reliance on problematic chronic opioid therapies. Transcranial Direct Current Stimulation (tDCS) is a novel, minimally-invasive brain stimulation technique that demonstrates analgesic effects when applied over the dorsolateral prefrontal cortex (DLPFC). Accumulating data from our group and others suggest that tDCS may augment the treatment effects of CBT for chronic pain and perhaps comorbid sleep disturbance. However, no studies to date have directly investigated potential synergistic effects of combining these therapies on pain, sleep, and opioid misuse. With the use of sophisticated actigraphy monitoring, and the knowledge and skill of sleep experts within the Sleep and Anxiety Treatment and Research Program (SATRP) at MUSC, the proposed study directly addresses a gap in the literature by testing the feasibility and preliminary efficacy of tDCS in combination with CBT to reduce pain, improve sleep, and limit the severity of prescription opiate use disorders among U.S. military Veterans and their family members with CLBP and co-morbid prescription opiate use disorders. tDCS may prime and modulate prefrontal circuitry resulting in enhanced capacity to tolerate and down-regulate the emotional component of pain experience, while CBT can teach the skills necessary to maintain these gains, thus resulting in a synergistic effect.

The primary objectives of the proposed Stage II study is to evaluate the effects of CBT in combination with tDCS in (1) improving pain and functionality, (2) reducing severity of opioid use disorders, and (3) reducing impairment in associated mental health areas (e.g., depression, anxiety, PTSD), with a novel focus on the role of sleep disturbance as a consequence, predictor and potential mediator of chronic pain. This study will also yield valuable data regarding the potential of CBT (with and without tDCS augmentation) to improve sleep in the context of chronic pain and opioid misuse. We will also determine the effects of treatment on neural activity in cognitive and limbic brain regions involved in pain regulation using functional magnetic resonance imaging (fMRI), and examine its relationship to sleep latency, total sleep time, sleep efficiency and opioid use severity. Secondary objectives are to evaluate acute lab-based pain markers and neural correlates of improvement in chronic pain using quantitative sensory testing. In order to accomplish this we are: using a manualized, evidence-based CBT intervention that is already widely-disseminated within the VA system; employing a randomized, between-groups, double-blind experimental design; and examining standardized, repeated, dependent measures of change in: (a) clinical outcomes such as pain, opioid and other substance use disorders (e.g., alcohol, illicit drugs, other prescription drugs), depression, anxiety, sleep and PTSD symptomatology; and (b) process variables such as participant satisfaction, quality of life and treatment retention.

The following specific aims are proposed:

Specific Aim 1: To compare the efficacy of CBT + real tDCS vs. CBT + sham tDCS, in reducing pain and improving sleep.

Specific Aim 2: To compare the efficacy of CBT + real tDCS vs. CBT + sham tDCS, and the potential mediating effects of sleep in reducing severity of prescription opiate use disorders, as well as impairment in associated areas (i.e., other substance use disorders, depression, anxiety, PTSD).

Specific Aim 3: To use fMRI to determine the effects of CBT (with and without tDCS) on the neural response to pain and its relationship with opiate use severity.

The proposed study will answer critical questions regarding the ability of tDCS to augment the effects of CBT for pain, and elucidate possible mechanisms underlying improved outcomes. tDCS is inexpensive and highly portable, making it a very scalable tool to add to current CBT interventions within the VA healthcare system. Additionally, the proposed measurement (via actigraphy monitors) of sleep patterns will allow investigators to examine the impact of these investigational treatments on sleep patterns, the temporal co-variation in sleep and pain, and potential mediation effects of sleep on pain and opioid misuse. This study has the particular advantages of building directly on positive preliminary findings among civilians and is being led by a multi-disciplinary team of experts who have successfully collaborated in the past and are uniquely qualified to implement this type of investigation. The results of this study will provide important information and a more comprehensive and rich picture of pain, sleep, opioid-use and functioning in the context of a highly novel and innovative non-pharmacologic and evidence-based intervention combination (CBT and tDCS), and will help inform policies and programs to better serve the needs of U.S. military personnel, Veterans, and their families. The findings from this study may help reduce public health costs and morbidity/mortality associated with chronic pain and co-morbid prescription opiate use disorders among our nation's Veterans.

OVERVIEW: Military personnel and Veterans have significantly higher rates of chronic pain than the general population. If left untreated, Veterans with chronic pain are at risk for psychiatric problems (e.g., substance use disorders, depression, anxiety, sleep impairment), suicidal ideation and attempts, increased mortality, reduced resiliency, unemployment, and family/couples impairment. Although opioid analgesics are effective for acute pain, there is an over-reliance on opioid therapies to manage chronic pain, which leads to increased risk of opioid misuse and dependence in Veterans. Thus, there is a critical need for non-pharmacologic approaches to manage chronic pain in Veterans. Cognitive behavioral therapy (CBT) is widely used for pain; however, its effects are modest when used in isolation. The proposed project is designed to test the ability of an innovative, minimally-invasive brain stimulation technique (tDCS) to augment the effectiveness and durability of CBT for pain to reduce pain, improve sleep, and limit the severity of prescription opiate use disorders among U.S. military Veterans and their family members with CLBP and co-morbid prescription opiate use disorders.

SIGNIFICANCE

Chronic Pain and Opiate Use among Veterans. Between 50% and 80% of Veterans suffer from chronic (≥ 3 months) pain and the majority of Veterans with chronic pain report a primary diagnosis of chronic low back pain (CLBP).[1-4] Use of prescription opiates for the treatment of musculoskeletal pain doubled over the past decade, and diagnosis of CLBP is associated with very high rates of opioid prescribing in VA clinics. [3] Both licit and illicit use of opioids is growing, driven partially by an increased reliance on opioids for the treatment of chronic pain.[1-5,38,40,41,83] In spite of the over-reliance on chronic opioid therapy, there is a lack of evidence supporting long-term efficacy [5, 6] and substantial evidence demonstrating problems such as analgesic tolerance, physical dependence, opioid-induced hyperalgesia, and risk of misuse, addiction, diversion, overdose and death.[84] Opioid misuse has increased dramatically over the past decade, and opioids now surpass cocaine, heroin, methamphetamine, and marijuana as a leading drug of new abuse.[8-9,85] Data from our group and others show that chronic pain complaints are common among individuals with opioid use disorders, and many report that their opioid use first began with a legitimate prescription for pain and subsequently progressed to misuse and addiction[86-88,7], making it important that prevention and intervention efforts target primary care settings. In summary, while pain management services are in place for Veterans, substantial gaps exist and non-pharmacologic evidence-based interventions that effectively address pain and comorbid prescription opiate use disorders are vitally needed in VA-based healthcare settings.

Chronic Pain and Sleep. There is now appreciable evidence that sleep is a significant factor related to chronic pain development and maintenance, especially among patients with idiopathic low-back pain. [75] [76-78] The estimated prevalence of poor sleep in patients with non-specific chronic low back pain is estimated to be 64% and the annual cost for musculoskeletal pain and reported poor sleep is estimated to be billions of dollars annually in the US. [76]. More data is needed to elucidate the relationship between sleep and chronic pain. Our knowledge about mechanisms of action and mediators of therapeutic benefit among new treatments that have the potential to impact pain and opioid use may be enhanced significantly by careful examination of sleep patterns. The integration of more sophisticated methods for sleep measurement will yield valuable data regarding the relationship between sleep and chronic pain as well as permit examination of sleep as potential mediator of therapeutic change in chronic pain and opioid misuse.

Cognitive-Behavioral Therapy (CBT) for Chronic Pain. Chronic pain is a complex disorder which involves sensory-discriminatory, motivational-affective and cognitive-evaluative processes[8], presenting both cognitive and biological targets for intervention. CBT is the most widely supported, evidence-based non-pharmacologic treatment for CLBP.[9] A number of well-controlled studies demonstrate that CBT is efficacious in the reducing pain. [10-12] [13] The CBTs employed in these studies generally consist of cognitive coping strategies (e.g., distraction, relabeling, reducing pain-catastrophizing) and self-management/relaxation strategies designed to enhance perceived control and reduce sympathetic tone. Overall, these studies provide good evidence for the efficacy of CBT in comparison to attention placebo, patient education, symptom monitoring and/or no treatment control conditions. However, a recent meta-analysis of CBTs for CLBP indicates significant room for improvement, specifically with respect to intermediate and long-term pain management.[9] Furthermore, the brain mechanisms responsible for observed effects related to CBT are poorly understood.

Brain Pathways Associated with CBT for Pain. Pain catastrophizing (i.e., cognitive characterizations of pain as awful, horrible and unbearable) is increasingly being recognized as an important factor in the experience of pain. Catastrophizing appears to augment pain by enhancing attention to painful stimuli and heightening limbic circuitry responses. [14] Catastrophizing has been shown to be associated with activity in multiple regions involved in both the cognitive (dorsolateral prefrontal cortex; DLPFC) and limbic aspects of pain processing, including the anterior cingulate cortex (ACC) and medial frontal cortex.[14] CBT for pain may decrease activity in these limbic brain areas via activation of the ventrolateral prefrontal/lateral orbitofrontal cortex[15]. Preliminary data from our laboratory suggests that lower activity in limbic brain regions is directly related to elevated activity in the DLPFC, which is involved in cognitive control. This suggests that CBT may activate a cortical control mechanism over pain experience. Therefore, increased DLPFC activation via *brain stimulation techniques* (like tDCS) may provide a reinforced cortical governance signal to limbic regions,[16] which might result in reduced pain symptoms, longer-term benefit and improved cognitive coping (Aim 1). Preliminary data from our group demonstrate that prefrontal brain stimulation applied to the DLPFC during the receipt of CBT results in increased pain tolerance and cognitive perceptions of control. The proposed study is designed to build directly on these preliminary findings, and further examine mechanisms of action using functional magnetic resonance imaging (fMRI) techniques pre and post treatment.

Brain Pathways in Pain and Addiction. Left DLPFC activation has been found to negatively correlate with pain unpleasantness and pain catastrophizing[17] [18], suggesting a governing role of the prefrontal cortex over pain experience. Additionally, recent studies suggest that cognitively-mediated analgesia involves μ-opioid systems in the brain[19] and is associated with decreased activation of the ACC and insula. These effects correlate with prefrontal cortex activation.[20] Thus, DLPFC activation might result in analgesic effects, presumably by attenuating the limbic response to pain (specifically in the ACC and insula, Aim 3). [21] [22] [23]

Chronic pain patients may be particularly vulnerable to opioid use disorders through a process that involves dysregulation of emotional and cognitive systems, as well as deficits in inhibitory control.[105] The ventral tegmental area (VTA)/nucleus accumbens (NAcc) pathway underlies euphoria and reinforcement, but is heavily modulated by cortical structures responsible for learning and decision-making. The corticostriatal network of reward processing involves cognitive interpretation of reward-related cues in the DLPFC.[90] The analgesic and euphoric properties of opioids are mostly mediated by μ-opioid receptors, which can be found in pain processing regions like the DLPFC, ACC, insula and amygdala. Attention and expectations are among the executive functions associated with DLPFC that can alter pain perception and drug craving. [17, 24, 25] [20, 26, 27] [28] Taken together, the existing literature on the role of DLPFC in modulation of pain and reward-related neural activity suggests that DLPFC stimulation may directly impact pain and motivation to use/abuse opiates.

Effects of Brain Stimulation on Pain and Addiction. Several studies from our laboratory and others show that stimulating the DLPFC with transcranial direct current stimulation (tDCS) or transcranial magnetic

stimulation (TMS) reduces experimentally-induced, acute, and chronic pain[29-40] (see Preliminary Studies section). We have also conducted several pilot studies demonstrating that DLPFC stimulation reduces drug and food craving. tDCS has several advantages over TMS and other brain stimulation techniques as it is portable, less cumbersome to administer, significantly less expensive (approximately $400-450 per device vs. >$100,000 per machine), has fewer known risks, may have longer-lasting effects on cortical function, is quieter, and has less associated patient discomfort. [41, 42]

Dr. Borckardt (PI) and members of the investigative team have conducted several pilot studies to examine the effects of DLPFC stimulation on methamphetamine, nicotine and food craving. In a single-blind, sham-controlled crossover study, 10 methamphetamine (MA)-dependent individuals and 8 healthy controls were randomized to receive 15 min of sham or real anodal stimulation of the left DLPFC via TMS. Anodal tDCS increases the excitability of the stimulated brain area, while cathodal tDCS decreases it. [43 44 45 46] During each session, participants were exposed to blocks of neutral and MA-associated cues. In MA users, real left DLPFC cathodal stimulation increased self-reported craving as compared to sham). These findings suggest that inhibition of the left DLPFC may increase drug craving by inhibiting the prefrontal cortex and/or indirectly activating subcortical regions involved in craving. In a related study, 16 nicotine-dependent participants were randomized to receive real high-frequency (activating) rTMS or sham over the left DLPFC. [47] The participants received cue exposure before and after TMS and rated their craving after each block of cue presentation. Stimulation of the left DLFPC with real, but not sham, TMS reduced nicotine craving significantly from baseline. When compared with neutral cue craving, the effect of real TMS on cue craving was significantly greater than the effect of sham TMS. Our group has also shown that activation of the left DLPFC via tDCS reduces craving for food and enhances ability-to-resist foods among high-food-craving individuals. [48] This study employed a randomized within-subject crossover design in which participants received real and sham tDCS and were blind to the condition. The percent change in craving and ability to resist food from pre- to post-stimulation was significantly greater for real tDCS vs. sham stimulation.

In a recent study,[49] pain thresholds to electrical stimulation were assessed in 20 healthy individuals who received anodal tDCS. Four conditions of stimulation were compared: motor cortex (M1), DLPFC, occipital cortex, and sham. Results suggest that DLPFC tDCS can modulate the perception of pain via mechanisms independent of sensory perception. [49] An adjunctive study with 22 healthy individuals showed that anodal tDCS of the DLPFC (but not M1, occipital, or sham) decreased perception of unpleasantness and emotional discomfort/pain while subjects viewed aversive images.[50] While existing research shows analgesic effects of DLPFC stimulation in neuropathic pain, post-surgical pain, and laboratory-induced pain, and numerous studies support the efficacy of CBT for chronic pain, no published studies to date have combined these two intervention strategies. tDCS may prime and modulate prefrontal circuitry resulting in an enhanced capacity to tolerate and down-regulate the emotional component of pain experience, while CBT can teach the skills necessary to maintain these gains, thus creating a synergistic effect. By capitalizing on the effects of tDCS on prefrontal circuitry and combining them with CBT, we may achieve longer-term and more substantial pain reduction than with CBT alone. The present study represents a logical next step-forward in the development of non-pharmacologic interventions for the management of the chronic pain and commonly co-morbid conditions.

APPROACH

Overview: The proposed study is a Stage II double-blind, randomized controlled trial of the impact of combining tDCS with CBT in the treatment of CLBP in Veterans with co-morbid opioid use disorders. A repeated measures design with 2 intervention arms will be used: CBT + real tDCS vs. CBT + sham tDCS. Outcome measures allow us measurement of effects on pain, opioid use severity, as well as collateral mental and physical health (e.g., depression, other substance use, PTSD, quality of life).

Subjects: Participants will be 150 treatment-seeking Veterans or family members of Veterans (including National Guard and Reservists) between the ages of 18 and 70 with chronic pain BPI pain on average score≥4/10; ≥3 months duration of pain) and a prescription opiate use disorder (past 6 months; COMM score ≥7). Specific inclusion and exclusion criteria can be found in the Human Subjects Section. The actigraphy sleep measures will be gathered in ~90 (all participants that enroll going forward) of the planned 150 participants in our sample (~75% of the sample).

Recruitment: The primary recruitment site will be the outpatient Ralph H. Johnson's VAMC Pain Management Clinic (PMC). Data from 2012 indicate that 39,436 opioid analgesic prescription orders (exclusive of refills) were provided to 8,189 unique patients at our VAMC. To date, 2013 data indicate that 33,136 prescription orders (exclusive of refills) for opioid analgesics have been provided to 7,447 unique

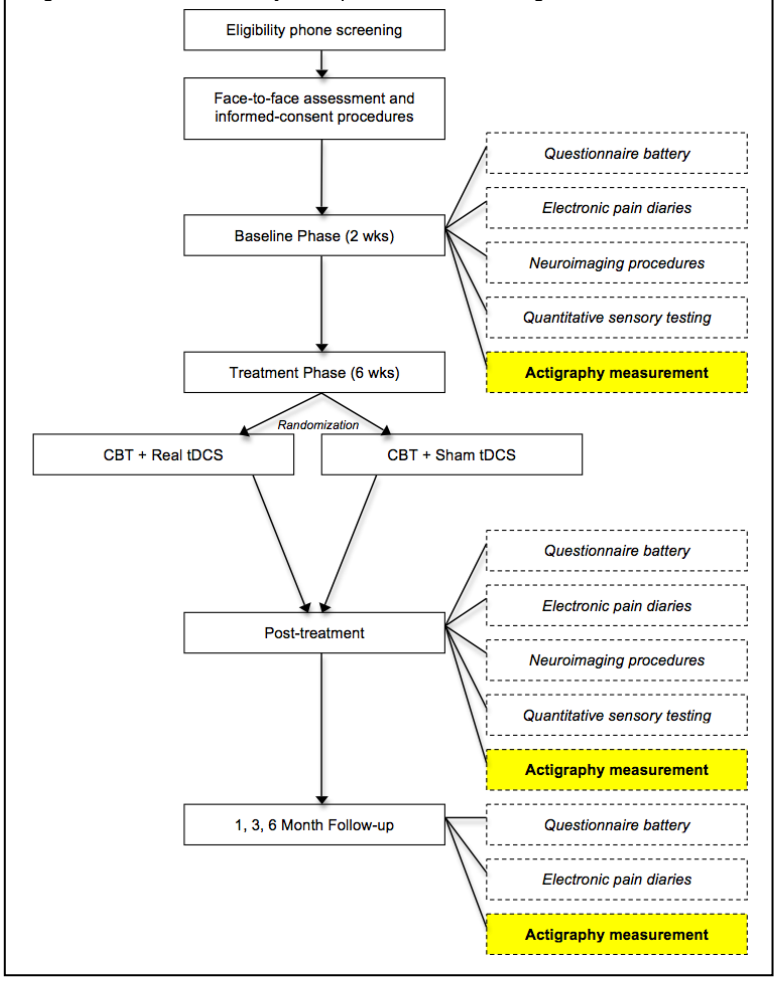
patients. Consults for pain management are made directly to the PMC's Interdisciplinary Pain Team, which includes an Anesthesiologist (Robert Friedman, MD), a Health Psychologist (Layne Goble, PhD; PMC Recruitment Liaison for this study), a Pharmacist (Anthony Abramczyk, PharmD; and nursing staff. Data from October 2012 – August 2013 indicate that the PMC completes approximately 68 new-patient pain consultations each month (816 new patients per year). Approximately 60% of all patients seen in the PMC have a diagnosis of CLBP (41 CLBP patients per month). For the proposed study, we need to enroll 24 Veterans or family members per *year*. As such, there should be no problem with adequate subject recruitment in order to complete the study within the timeline proposed. See the Facilities and Resources section for more information about the PMC.

While recruitment will be primarily from patients presenting to the VAMC's PMC, potential participants will be allowed to self-refer in response to signage on CARTA transit vehicles; newspaper, television and radio advertisements; research-specific websites (e.g., ResearchMatch.org, SCResearch,org, study site, etc.); and advertisements posted on social media sites (e.g., Craigslist, Facebook, Reddit, etc.). Furthermore, IRB-approved recruitment materials will be posted and/or disseminated across the community, as well as VAMC and MUSC clinics.

Letter of invitation: Additionally, Veterans and their family members may be recruited into this study via a letter of invitation. A list of patients with Veteran status at MUSC will be generated by the Epic Electronic Medical Records (EMR) interface for which the study PI has access. Epic is a user-friendly health information system, chosen by MUSC for implementation in its patient clinics beginning in December 2010. Additionally, a CPRS chart review of the patients in the VAMC Pain Management Clinic will be conducted. We will mail an invitation to participate to those who agree to be contacted for research. This letter will provide generic information about the study and a telephone number that interested subjects can call to receive detailed information. Patients that agree to participate will be scheduled for a screening visit.

General Procedures: Figure 5 illustrates the study flow, procedures and design. Participants will undergo brief screening over the phone to ensure they meet inclusion criteria. Participants self-referred from MUSC community flyers or other advertisements may select to complete a pre-screening tool via the web based platform "Redcap" to assess for initial eligibility. A face-to-face baseline assessment will be scheduled for eligible individuals at the VAMC (if recruited from this facility) or MUSC (if recruited from the population at large). Potential participants will be given a full description of the study procedures and asked to read and sign an IRB-approved informed consent form before any study procedures or assessments are conducted. Ineligible participants will be referred clinically for treatment. Consent will take place in a private office and will be conducted by trained staff, including the PI, Co-Is, Study Coordinator, and Research Assistant. Baseline screening will involve further verification of diagnostic conditions (opiate use disorder, depression, anxiety, PTSD, sleep), a medical history and physical exam, assessment of concomitant medications, and breathalyzer and urine drug tests. The medical history may be conducted via telehealth. If conducted via telehealth, Participants will be required to provide documentation of a recent blood pressure (BP) measure (past 6 weeks). If an at-home blood pressure cuff is available, the participant may take a reading during the virtual H&P (with PA or MD guidance).

Figure 5. Overview of study flow, procedures and design



Alternately, the participant can provide BP documentation from a medical professional (within the past 6 weeks) and/or a study team member can view the participant's EPIC/CPRS record for a recent BP value. Self-report measures of pain, opiate misuse, depression, anxiety, PTSD, and sleep functioning will also be assessed at baseline and throughout the study.

During the baseline phase, eligible participants will have their cell phones registered into the *daily diary system* described below and will be given instructions on how to respond to daily queries regarding pain, mood, craving, etc. Patients without a cell phone will be provided a cell phone for use during the study. Actigraphy monitors will be provided for all participants for sophisticated measurement of sleep patterns that will allow investigators to examine (1) the impact of the investigational treatments on sleep patterns, (2) the temporal co-variation in sleep and pain, and (3) potential mediation effects of sleep on pain and opioid misuse. Eligible participants will then complete a 2-week baseline period during which daily diary assessments are obtained. During the 2-week baseline phase, patients will undergo structural and functional MRI scanning and QST procedures (described in more detail in the Study Interventions and Procedures section). These procedures will be repeated at the end of treatment.

Immediately following the baseline period, subjects will receive 11, 60-min sessions of manualized, individual CBT for pain delivered once a week over approximately 11 weeks. Therapy sessions may be delivered via doxy.me with the subject in an MUSC office at a standard desk using a laptop computer. Subjects will be randomized to receive real or sham tDCS during the therapy sessions. Within 3 weeks following completion of the CBT treatment, participants will repeat the neuroimaging and QST procedures. They will return at 1-, 3-, and 6-months post-treatment for follow-up visits. If participants are not able to return in person for the follow up visits, participants can complete the follow up assessments on REDCap, entered directly into the online portal to ensure security and prevent data loss.

Actigraphy measurement of sleep patterns will be recorded after the 2-week baseline period, post treatment, and at 1-, 3-, and 6-months post-treatment follow-up visits.

Setting: All procedures will be conducted on the MUSC campus or in VA research offices. Treatment procedures can be conducted via telehealth in an MUSC office.

Telehealth: Participants can complete therapy sessions via MUSC/VA approved video telecommunication platforms (doxy.me). Therapy sessions will be delivered in a private office via laptop computer running MUSC/VA approved applications. This will allow the therapist to communicate with the participant from a separate room.

Assessment Instruments: After the informed consent procedure, subjects will complete a battery of assessments. The instruments to be used (Table 1) were selected because many are standardized, have good psychometric properties, are widely used and have been used by our research group, and many are outcome measures recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT). [66, 67]

Primary Outcome Measures: The primary measures are described in this section. Information regarding additional measures can be found in Table 1. (1) **Pain:** *Electronic Daily Diaries* will be administered using either standard feature or smart cell phones. The MUSC Technology Applications Center for Healthful Lifestyles (TACHL), directed by Dr. Frank Treiber (Co-I), will adapt software they originally configured for a daily monitoring protocol of PTSD symptoms. The pain/mood/craving/opiate-use questions will assess daily (via numeric rating scale; NRS) average pain, pain at its worst, pain unpleasantness, mood, activity-level, sleep quality, hours of sleep, opiate cravings, and will assess amount of prescription opiate. TACHL developed a SMS (Short Message Service)/MMS (Multimedia Messaging Service) encrypted gateway which enables ecological momentary assessment of pain, craving, etc. This communication system was selected due to its flexibility and ready availability for use on all cell phone types and their carriers. Measures will be collected at random times during waking-hours each day to minimize response bias associated with event-related reporting. See the Facilities and Resources section for more information on TACHL. The *Brief Pain Inventory (BPI)* is a widely used, 17-item self-report measure that assesses pain intensity and interference. Patients rate pain severity as well as the degree to which pain interferes with seven aspects of life: Work, Activity, Mood, Enjoyment, Sleep, Walking, and Relationships. (2) **Opiate Use Severity:** The *Current Opioid Misuse Measure (COMM)*[68, 69] is a brief, 17-item measure designed to monitor chronic pain patients on opioid therapy. It assesses medication misuse behaviors such as, obtaining additional opiates from other doctors or the emergency room; taking medication that belongs to someone else; taking more opiates than prescribed; using opiates for alternative reasons (e.g., to reduce anxiety); consuming opiate medication via alternative route

(e.g., crushing and snorting). The COMM instructions will be modified to utilize a 7-day, 60-day, and 90-day window and will be used as a weekly assessment in the proposed trial. The *Timeline Follow-Back (TLFB)* [70] obtains retrospective self-report of substance use by using a calendar and other memory prompts to stimulate recall. Quantity and frequency assessments can be made using this instrument, as well as time-to-event measures. The TLFB yields consistently high test-retest correlations and correlates well with other self-reports and collateral reports.[71] The TLFB will assess use (quantity and frequency) of prescription opiates, alcohol, nicotine, illicit drugs (e.g., cocaine, marijuana), and other prescription drugs (e.g., benzodiazepines).

Secondary Outcome Measures: The secondary measures are described in this section. Secondary efficacy endpoints are abstinence and retention rates, and psychometric scales (e.g., Beck Depression Inventory, Addition Severity Index), which will be included and used to gain insight into potential effect modification and mediation. Actigraphy monitors, provided for all participants at enrollment, will yield objective measures including Raw Acceleration, Energy Expenditure, MET Rates, Steps Taken, Physical Activity Intensity, Activity Bouts, Sedentary Bouts, Heart Rate R-R intervals, Body Position, Sleep Latency, Total Sleep Time, and Sleep Efficiency.

Table 1. Assessment Instruments and Timeline

Instrument name	Purpose/Domain	Time	BL	1	2	3	4	5	6	7	8	9	10	11	FU 1,3,6
Informed Consent	Obtain informed consent	10 min	X												
Medical History and Physical Examination	Assess participant physical condition	30	X												
Demographics	Characterize sample	5 min	X												
Locator Form	Locate participants	5 min	X												
MINI 7.0 DSM-V criteria	Assess DSM-V psychiatric disorders	40 min	X												
Brief Pain Inventory: BPI	Primary Outcome; pain severity and functional impairment	10 min	X	X	X	X	X	X	X	X	X	X	X	X	X
Current Opioid Misuse Measure: COMM	Primary Outcome; prescription opiate use disorder severity	5 min	X	X	X	X	X	X	X	X	X	X	X	X	X
Timeline Follow-Back: TLFB	Primary Outcome; prescription opiate and other substance use	10 min	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Drug Screen: UDS	Assess illicit drug use	5 min	X	X		X		X		X		X		X	X
Alcohol Breathalyzer	Assess alcohol use	5 min	X												
Urine Pregnancy Screen	Assess pregnancy	5 min	X												
Pain Coping Inventory: PCI	Assess pain coping behaviors	10 min	X						X					X	X
ShortForm36 Health Survey: SF36	Assess quality of life	10 min	X											X	X
PTSD Checklist-Military: PCL-M	Assess PTSD symptoms	10 min	X											X	
Beck Depression Inventory: BDI-II	Assess depression	1 min	X	X	X	X	X	X	X	X	X	X	X	X	X
Beck Anxiety Inventory: BAI	Assess Anxiety	1 min	X	X		X		X		X		X		X	X
Pittsburgh Sleep Quality Index: PSQI	Assess sleep functioning	5 min	X											X	X
Pain Catastrophizing Scale (PCS)	Assess the impact of catastrophizing	3 min	X	X		X		X		X		X		X	X
Patient Health Questionnaire: PHQ-15	Assess health status	10 min	X						X					X	X
Pain Treatment History	Monitor services utilization	10 min	X												
Charleston Psychiatric Outpatient Satisfaction Scale	Assess patient satisfaction	5 min												X	
Helping Alliance Questionnaire: HAQ-II	Assess therapeutic alliance	5 min												X	
Helping Alliance Questionnaire: HAQ-II	Assess therapeutic alliance	5 min												X	
Treatment Tracking Services Form	Assess changes in TX	1 min	X	X	X	X	X	X	X	X	X	X	X	X	X

Participant Feedback Survey	Assess participant study experience	3 min											X	
Best Guess Questionnaire	Assess tDCS blind integrity	1 min											X	

STUDY INTERVENTIONS AND PROCEDURES

Overview: Subjects will be randomized to CBT + tDCS or CBT + sham tDCS, which are described in the following sections. Note that subjects will not receive any other CBT services during the study. All services received (e.g., self help groups, case management) will be carefully monitored and tracked at weekly visits. All subjects will receive actigraphy monitors at enrollment to passively assess sleep patterns.

Cognitive-Behavioral Therapy for Pain (CBT): All participants will receive 11, 60-min, manualized individual sessions of CBT for pain. We will use the therapy manual and accompanying patient workbook[72], which were developed by Dr. John Otis (Consultant; see *Letter of Support*) and are endorsed by the Department of Veterans Affairs and widely used nationally by the VA healthcare system. See Appendix A for the manuals. Examples of session topics include: education on chronic pain, diaphragmatic breathing and progressive muscle relaxation, automatic thoughts, cognitive restructuring, stress management, time-based pacing, pleasant activity scheduling, anger management, and sleep hygiene.

Therapist Training and Supervision: All therapists will be licensed Masters or Doctoral level clinicians with experience delivering CBT. During the lead-in/preparation phase of the study, therapists will receive extensive training in the CBT treatment protocol lead by Drs. Borckardt, Bottonari and Otis. Dr. Otis is the developer of the CBT manual being employed in this study. Study therapists will complete four phases of training: (1) didactic review of intervention-specific theory; (2) manual review; (3) a 2-day training workshop and (4) subsequent completion of one to two pilot study case in which all sessions will be recorded and rated for therapist adherence and competency. Throughout the study, therapists will receive weekly supervision conducted by Drs. Bottonari and Borckardt focusing on manual adherence and competency, and clinical concerns about particular patients. If during the course of the study it is determined upon review of therapy sessions and supervisory sessions that a therapist is not competent or does not adhere sufficiently to the manual, the therapist will be replaced. The decision to replace a study therapist will be a conjoint decision made by Drs. Borckardt, Bottonari, and Brady.

Adherence Ratings: Finally, to assure that the therapy is delivered in a manner consistent with manual guidelines, all therapy sessions will be recorded and randomly selected sessions (25% of therapy sessions) will be evaluated using methods developed by Hollon and colleagues[73] in the NIMH Collaborative Study. Interrater reliability on measures of adherence and competence between raters will be established.

Transcranial Direct Current Stimulation (tDCS): 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 11 CBT sessions. Each subject's high-resolution structural MRI image will be transformed into normalized MNI space. A standardized BA map will be overlaid onto the normalized participant brain image. A custom-developed software program will then reverse transform the colorized participant brain image back into its original dimensions. The participant's color-tagged brain image will be imported into the Brainsite frameless sterotaxic system and registered to the participant in the Brain Stimulation Laboratory. BA9 will be identified (by color) and marked with a trajectory-target in the Brainsite system. Participants will be fitted with a thin Lycra cap and the left and right DLPFCs will be marked with a felt-tipped marker. Small holes will be punched in the Lycra caps in the left and right BA9 positions. Before each therapy session, the cap will be re-placed, a nontoxic felt-tipped marker will be used to mark the targets on the participant's scalp, the cap will be removed, and the electrodes will be attached with Velcro straps. The pre-session tDCS set-up will take approximately 10 minutes.

Figure 6. tDCS Device

Participants will undergo 11 sessions (30-min each) of real or sham tDCS conducted with the Phoresor-II Auto (Model PM850, Iomed, Salt Lake City Utah, USA; Fig. 6) 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 programmed treatment duration. A tDCS technician, hired specifically for this study, will be responsible for scalp marking, electrode placement and device management. tDCS (real or sham) will be delivered during the middle 30 minutes (i.e., minutes 15-45) of each 60-minute CBT session. Thirty minutes is approximately the maximum duration of tDCS delivery that keeps skin-damage risk at a minimum. The density and total charge delivered by the selected parameters is consistent with those used safely in our and other

investigators' use of tDCS. A very low dose (0.125mL) of topical benzocaine (6%) cream will be applied to the skin beneath the sponge electrodes. After each therapy session, a vitamin-E/aloe cream will be applied to the skin under the electrodes to reduce risks associated with skin drying. The investigative team has conducted over 800 tDCS sessions using these methods with no adverse or serious adverse events.

Specialized software allows for the tDCS device to be switched on and off (i.e., real vs sham) without any intervention from the patient or experimenters. This will be controlled via a silent solid-state relay driven by an Ontrak ADU218 (Ontario, Canada). For sham tDCS, the stimulator will be turned off automatically following 45s, whereas the stimulation will be maintained for 30-min in the real tDCS group. The sham stimulation mimics the transient scalp sensation perceived when the stimulator is initially switched on. This technique is currently state-of-the-art for conducting convincing sham stimulation in the tDCS field, and our pilot data show that patients are unable to accurately distinguish real from sham tDCS. Randomization will be accomplished via custom-developed software that will export a condition-randomization file, coded by subject-ID-number, directly to the Ontrak control software. The randomization will be encoded in the software so that the operator enters a patient-number to start stimulation without knowing whether those specific numbers area associated with active or sham tDCS.

Neuroimaging Procedures: Functional MRI (fMRI) data will be acquired from all participants 1 week before and within 3 weeks of completion of the 11-session CBT protocol. The scans will be conducted at the MUSC Center for Biomedical Imaging, which is also designated as VA-approved space. High-resolution structural scans will be obtained at the beginning of each session using an inversion recovery 3D spoiled gradient echo (3DSPGR) sequence, 128 slices, matrix size: 256 x 256, field of view: 24 cm, section thickness: 1.5 mm with no gap between sections, giving an in-plane resolution of 0.94 mm. This sequence will be used for anatomic overlays of the functional data, for spatial normalization to a standard atlas, and subsequent voxel-based morphometry (beyond the scope of this proposal). Outside the scanner, participants will undergo a thermal method-of-limits procedure (aided by parameter estimation by sequential testing) to determine the temperature output required from the Medoc Pathway System to reliably produce a subjective NRS pain rating of 7/10. This temperature will be delivered in 12-second tonic blocks interspersed with 18-second rest/pain rating periods during the fMRI sequence. The data will be preprocessed in accordance with standard practice in our laboratory using SPM 8 (Wellcome Department of Cognitive Neurology, London, UK) and the average time courses from anatomically defined regions of interest (ROIs) extracted and analyzed using customized scripts (Matlab 6.5, Mathworks, Natick, MD).

Quantitative Sensory Testing (QST): Secondary objectives of the study are to evaluate acute lab-based pain markers. QST provides indices of changes in specific peripheral and central nociceptive and proprioceptive processing. Using QST we will assess: (1) *mechanical pain threshold* using the IITC Life Sciences Digital Anesthesiometer applied to the distal phalange of the digiti minimi of the left hand (increased at rate of 10grams/sec; pressure recorded in grams). (2) *thermal pain tolerance* using 5 trials of cutaneous heat stimuli via the ATS thermode. (3) *thermal wind-up pain* will be assessed with the CHEPS thermode, which will deliver 20 brief (0.75s) suprathreshold thermal stimuli selectively stimulating C-fibers. During 30sec of repeated heat stimulation, subjects will indicate their level of pain severity using a visual analogue scale. This QST paradigm will provide preliminary data about any selective effects of the interventions on A-∂, A-ß, and C-fiber activation as well as yield preliminary mechanistic information about unique effects of CBT+tDCS on sensory versus affective dimensions of the pain experience.

Sleep Monitoring: Participants will be given actigraphy monitors at the time of study enrollment that employ a validated 3-axis accelerometer and data filtering technology, and contains a gyroscope, magnetometer, and secondary accelerometer to deliver valuable information about movement, rotation, and body position. The objective measures yielded by the device include: Raw Acceleration, Energy Expenditure, MET Rates, Steps Taken, Physical Activity Intensity, Activity Bouts, Sedentary Bouts, Heart Rate R-R intervals, Body Position, Sleep Latency, Total Sleep Time, and Sleep Efficiency. An advanced wear time sensor on the back of the device uses capacitive touch technology to automatically detect when a wrist worn device has been removed for simplified compliance monitoring and data cleaning. We will primarily be gathering daily information regarding sleep latency, total sleep time and sleep efficiency. This information will permit detailed examination of the role of sleep, chronic pain and opioid use among veterans and family members.

Compensation: Subjects will receive $40 for the baseline visit as well as an added bonus of $20 if they arrive on time; $20 for each therapy session, as well as a $50 bonus if all 11 therapy sessions are completed within 14 weeks of treatment initiation; $75 for each follow-up visit; $50 for each neuroimaging procedure; and $25 for each QST procedure. For each daily diary, they will receive $1. If all daily diaries are completed during

the 2-week baseline phase, they will receive an added bonus of $10. If all are completed during the treatment phase, they will receive an added $25. And if all are completed during the 1 month follow-up phase, they will receive an added $50. Thus, the total amount subjects may receive for the baseline assessment ($60), 11 therapy sessions ($220 + $50), 3 follow-up visits ($225), and pre- and post-treatment neuroimaging ($100) and QST ($50) testing as well as daily diary assessments ($14 + $10 for 2-week baseline, $77 + $25 for 11 weeks of treatment, $30 + $50 for the 1 month follow-up, $60 for the 3 month follow-up, and $90 for the 6 month follow-up.) = $1061. Additionally, subjects will be invited to participate in the recruitment of other subjects for this study. If subjects chose to participate, they will be provided with cards that they may give to other people (e.g., friends, acquaintances) who they think would be eligible and interested in this study. Subjects may choose to tell people to whom they give these cards to call the study office if they are interested in participating in the study. These individuals will not be identified unless they contact the study office themselves. If any of the cards they are given result in successful study recruitment, they will receive $20 for each referred individual who consents to participate in the study. Participation in the recruitment process is completely voluntary and if they elect not to participate, their participation in this study will not be affected in any way. Compensation will be in the form of cash, check, or ClinCard by Greenphire. If the subject choses to be compensated via check, it will be mailed to the address provided by the subject.

STATISTICAL ANALYSES AND POWER

Randomization: We will stratify randomization by (1) severity of opiate use (COMM score) and (2) pain severity (BPI score). Urn randomization will be used to balance the randomization assignment with respect to these strata. The purpose of stratification is to distribute these potential prognostic factors equally across treatment groups.

Intent-to-Treat Analyses. All analyses will be performed on two samples: (1) the intent-to-treat sample consisting of all randomized subjects and (2) the completers sample consisting of all subjects who complete at least 7 out of 11 sessions.

Missing Data. We will perform attrition analyses on whether participants and dropouts differ on key variables (symptom severity) and whether variables on which they differ interact with treatments to affect outcome measures. As participants will be randomized to treatment, it is unlikely that missing data will produce biased estimates of treatment effect, as observed and unobserved covariates should theoretically be balanced across treatment groups. In addition, in general, less than 10% missing data have little impact upon study power and do not introduce bias, regardless of the missing data mechanism.[74] Larger proportions of data missing at random (MAR) or missing not at random (MNAR) could potentially bias study findings and reduce power. If the percent missing data are greater than 10%, propensity score methods will be used for data imputation. In the propensity score method, first the distribution of the missing indicator variable given the observed data is modeled to derive a propensity score. Then observations are grouped on these propensity scores and an approximate Bayesian bootstrap imputation is applied to each group.

Time-Series Variables: The actigraphy devices will yield time-series data including sleep latency, total sleep time and sleep efficiency. Hierarchical Linear Modeling (HLM) will be applied to evaluate daily (time-series) pain, craving, opiate used, mood, anxiety, and physical activity ratings throughout the 3 phases of the study (baseline, treatment, and follow-up) and by group. The covariance structure of the model will be set to first-order autoregressive and independent effects of treatment on average daily pain will be assessed by controlling for daily fluctuations in craving, mood, anxiety, and activity in the model. Additional co-variates of CBT-related effects will include therapeutic alliance and pain coping styles. Additionally, cross-lag correlational analyses will be conducted on pain, craving, mood, anxiety, and activity data to estimate temporal order of changes during the trial.

Repeated Measures Variables: BPI, COMM, as well as mean weekly sleep latency, total sleep time and sleep efficiency scores will be examined with HLM using an unstructured covariance matrix. Subject-level intercepts will be entered into the model at level-1, and a time X group (real vs. sham tDCS) mixed model will be implemented. The primary model parameter of interest will be the time X group interaction term; however, main effects will be specified in the model. Effects of treatment on pain and opioid misuse will be separated from mood effects by co-varying mood and anxiety ratings at the individual subject-level.

Power: Effect sizes (Cohen's d) for CBT for chronic pain range from 0.3 to 1.4. A realistic effect-size estimate for the CBT intervention would be categorized as "medium/modest" (d=.5). The effect-size associated with clinical effects of tDCS on chronic pain in the current literature is also medium/modest (d=.5). With 150 subjects (75 in each group), power to detect effects (alpha=.05, effect-size d=.5, r among repeated measures=.5) is good to excellent (1-ß = .80 and .99, respectively). Power will be higher for the HLM model as sources of intra-class variability are better managed.

fMRI power to detect effects for planned contrasts was estimated as function of N, mean difference in percent signal change between block/conditions (μ_D), within-subject variability over time (∂_W), and between subject variability (∂_B) based on previous work conducted by our group. The effect size for our previously employed pain minus rest contrast was 1.8. Thus, power (1-ß) reaches .80 with only 12 participants per group (two-tailed, alpha=.01). The present study is therefore well-powered to identify significant connectivity and activation patterns using the pain-rest block paradigm and functional connectivity methods proposed.

Hypotheses: The hypotheses and statistical approaches for testing each hypothesis is as follows:

Hypothesis 1a: CBT + real tDCS will result in significantly greater improvements, as compared to CBT + sham tDCS, in average daily pain (electronic diary), pain unpleasantness (electronic diary) and functional impairment due to pain (BPI). To test this hypothesis, time-series analysis of diary average pain and pain-unpleasantness ratings will be conducted and BPI total scores will be used as repeated measures variables using the HLM methods and model co-variate strategies delineated above.

Hypothesis 1b: CBT + real tDCS will result in significantly greater improvement, as compared to CBT + sham tDCS, in sleep latency, total sleep time and sleep efficiency. To test this hypothesis, time-series analysis of actigraphy sleep latency, total sleep time and sleep efficiency values will be used as repeated measures variables using the HLM methods and model co-variate strategies delineated above.

Hypothesis 1c: Sleep latency, total sleep time, and sleep efficiency will improve significantly after the manualized CBT module devoted to sleep hygiene compared to other CBT modules. To test this hypothesis, interrupted time-series analysis (via HLM) will be conducted with the "Sleep Hygiene" CBT module established as the temporal demarcation point.

Hypothesis 1d: Time-series data representing sleep latency, total sleep time and sleep efficiency *improvements* will lead any observed *improvements* in pain and functioning consistent with emerging data on the temporal relationship between sleep and pain. [79] To test this hypothesis, lead-lag analysis of key time-series variables (sleep latency, total sleep time and sleep efficiency, pain and functional impairment due to pain) will be conducted.

Hypothesis 2a: CBT + real tDCS will result in significantly greater reductions, as compared to CBT + sham tDCS, in COMM scores and opiate craving ratings (electronic diary) compared to CBT + sham tDCS. To test this hypothesis, time-series analysis of diary ratings of opiate cravings will be conducted and COMM total scores will be used as repeated measures variables using the HLM methods and co-variate strategies delineated above.

Hypothesis 2b: CBT + real tDCS will result in significantly greater reductions, as compared to CBT + sham tDCS, in depression (BDI-II), anxiety (BAI), PTSD (PCL-M) and sleep (PSQI). To test this hypothesis, total scores on the identified measurements will be used as repeated measures variables using the HLM methods and co-variate strategies delineated above.

Hypothesis 2c: Total sleep time will mediate the clinical benefits of combined CBT-tDCS on chronic pain. To test this, structural equation modeling (SEM) will be used to examine the amount of variance explained in clinical improvement related to tDCS+CBT with and without total sleep time entered into the temporally dynamic model.

Hypothesis 3a: At baseline, percent BOLD signal change in the left DLPFC during pain blocks will be inversely related to BOLD signal in the left insula, ACC, thalamus, caudate, putamen, and medial prefrontal cortex.

Hypothesis 3b: After treatment, percent BOLD signal change in the left DLPFC during pain blocks will be significantly greater in the CBT + real tDCS group as compared to CBT + sham tDCS.

Hypothesis 3c: Functional connectivity between the left DLPFC and insula and ACC after treatment will be greater in participants who receive CBT + real tDCS as compared to CBT + sham tDCS.

Hypothesis 3d: The change in functional connectivity will be correlated with changes in pain (BPI), opiate use severity (COMM), and total sleep time.

For hypotheses 3a-3d, we will measure the following dependent variables: (1) percent change in BOLD signal in the left DLPFC as well as other limbic and executive regions of interest (ROIs) including the left and right insula, ACC, thalamus, caudate, putamen, and medial prefrontal cortex; and (2) functional connectivity (quantified as the average correlation coefficient between the ROIs) between the left DLPFC and the aforementioned ROIs will be used to test the hypothesis that CBT and tDCS have a synergistic effect on the neural adaptations in pain-control circuitry (i.e., insula and ACC). We will also investigate the functional connectivity with a negative control region (i.e., the primary visual cortex), which should not be differentially

modulated by either tDCS or CBT treatment. Group analyses will be performed using a random effects model (corrected, $p<0.01$ cluster level, $k= 25$, SPM 8).
Hypothesis 3e: Functional connectivity between the left DLPFC and insula and ACC after treatment will be greater in participants who receive CBT + real tDCS as compared to CBT + sham tDCS, and the change in functional connectivity will be correlated with changes in total sleep time.

HUMAN SUBJECTS RESEARH

Protection of Human Subjects

Risks to Subjects

Dr. Borckardt is a licensed clinical psychologist with extensive training and experience in conducting human research. The Co-Is also have extensive experience in human research, and Drs. Borckardt, George, Brady, McCauley, Barth, Hanlon, Santa Ana, and Flanagan have all completed the University of Miami computer-based CITI Human Subjects Research Education Course. All research activity, informed consents, and continuing reviews will be reviewed by MUSC's IRB in compliance with 45CFR46 before the research is started and continuing review will occur annually. The research staff will ensure that all information needed for the continuing review is at the IRB in accordance with IRB requirements.

Human Subjects Involvement and Characteristics

A total of 150 adults between the ages of 18 and 70 will be recruited over a 5-year period. The inclusion/exclusion criteria for the study are as follows:

Inclusion Criteria:

1. Ages 18 to 70.
2. United States Veteran or family member of a Veteran.
3. Able to provide informed consent and function at an intellectual level sufficient to allow accurate completion of the assessment instruments.
4. Subjects must be able to comprehend English.
5. Have a chronic pain condition and ≥3months duration of pain.
6. BPI score ≥4/10.
7. Meet DSM-5 criteria for current (i.e., past 6 months) prescription opioid use disorder (assessed via the MINI 7.0).
8. COMM score≥7.
9. Subjects may also meet criteria for a mood disorder if asymptomatic or anxiety disorders (PTSD, panic disorder, agoraphobia, social phobia, generalized anxiety disorder, or obsessive compulsive disorder). The inclusion of subjects with affective and anxiety disorders is essential because of the marked frequency of the co-existence of mood and other anxiety disorders among patients with chronic pain and prescription opioid use disorders.
10. Subjects taking psychotropic medications will be required to be maintained on a stable dose for at least four weeks before study initiation. This is because initiation or change of psychotropic medications during the course of the trial may interfere with interpretation of results.
11. Must consent to random assignment to CBT + tDCS or CBT + sham tDCS.
12. Must consent to complete all treatment and follow-up visits.
13. Must live within 100 miles of the Medical University of South Carolina.

Exclusion Criteria:

1. Subjects with symptomatic psychotic/bipolar disorder and/or deemed too high risk by the study physician
2. Subjects with current suicidal or homicidal ideation and intent.
3. Subjects with a current eating disorder (bulimia, anorexia nervosa) or with dissociative identity disorder, as they are likely to require specific time-intensive psychotherapy in addition to the proposed therapy for stabilization.
4. Subjects who would present a serious suicide risk or who are likely to require hospitalization during the course of the study.

5. Subjects enrolled in ongoing behavioral therapy for pain or substance use disorders, who are not willing to discontinue these therapies for the duration of the trial. Attendance at therapeutic activities other than study sessions will be closely monitored using the Treatment Services Review.
6. Subjects on maintenance anxiolytic, antidepressant, or mood stabilizing medications, which have been initiated during the past 4 weeks. If it is determined, based on clinical criteria, that a subject needs to be started on maintenance medications for anxiety, mood or psychotic symptoms during the course of the study, they will be discontinued from the treatment trial.
7. Subjects with organic mental syndrome.
8. Pregnant women.
9. History of seizures.
10. Implanted medical devices above the waist.
11. Latex allergy.
12. Diagnosis of Fibromyalgia.
13. History of eczema or other sensitive skin conditions.
14. Known brain tumors or lesions that intersect the area of stimulation.

Sources of Materials

Data will be in the form of structured clinical interviews, self-report rating scales and questionnaires, urine drug screen and breathalyzer tests, sleep monitoring, and neuroimaging data.

Potential Risks and Protection against Risks

Potential psychological risk includes exacerbations of distress during the assessment procedures or therapy sessions. Measures to avoid this include use of a CBT intervention that includes techniques to help reduce distress and anxiety, and improve mood (e.g., relaxation exercises, sleep hygiene, cognitive restructuring). Additional measures include informing subjects that they are free to terminate therapy sessions at any time. Risks associated with assessment include the possibility that subjects might be upset by questions pertaining to their emotional functioning, pain and physical challenges, and their substance use. Again, all subjects will be informed at the outset that they may terminate participation at any point. Our past research suggests that data collection using many of these measures can be conducted without undue psychological distress or exacerbation of symptoms among adult subjects. This experience includes substantial research with OEF/OIF Veterans and civilians with substance use disorders and chronic pain.

In the event that subjects experience extreme psychological distress secondary to participation, they will be encouraged to telephone the Principal Investigators (PIs). In addition, they will have access to urgent care services at the VAMC and MUSC. Any adverse effects noted by any project personnel will be immediately reported to the PIs, who will then report these adverse effects in writing to the IRB and NIH per protocol (see the Data and Safety Monitoring Plan at the end of this section for more details). The research team is comprised of several licensed clinical psychologists and psychiatrists with extensive experience working with adults who have experienced significant life stressors, drug/alcohol addiction and chronic pain. If project staff believes that a subject is significantly distressed by participation, the PIs will be notified and will contact the subject immediately to assess distress and assure subject safety. If called by subjects, the PIs will attempt to address all subject concerns and set up an alternate referral for counseling for those who desire it from outside the project.

All subjects will review, at the initiation of participation, an informed consent document which specifically reviews potential psychological distress as a potential outcome of participation. They will be asked to complete a safety plan and agree to call the project staff or 911 in the event they do not want to call project staff. However, if safety is in question in the minds of any project staff, the Mobile Crisis unit of Charleston County, which involves a team of police and psychiatric workers, will be dispatched to the subject's home to assure safety. In our ongoing clinical trials of Veterans with substance use disorders and PTSD (many of whom also have chronic pain), we have not had any problems related to participation that could not be safely resolved with these methods.

Because subjects are U.S. military personnel, absolute confidentiality of research records cannot be guaranteed. We will, however, make all possible efforts to protect the privacy and confidentially of study subjects. Subjects will be provided with a written informed consent document, which specifies the risks and confidentiality protections and limits of these procedures.

The risks associated with tDCS are minimal. There is no documented risk of seizure associated with tDCS, but participants with a history of seizure disorder will be excluded to ensure optimum safety. Side effects associated with tDCS include mild headache, tingling, itching, or stinging under the electrodes, and skin irritation.

After each therapy session, a vitamin-E/aloe cream will be applied to the skin under the electrodes to reduce risks associated with skin drying. The Investigators have conducted over 800 tDCS sessions with no adverse or serious adverse events.

The risks associated with Actigraphy monitoring are minimal. Some mild skin irritation or allergic contact dermatitis can occur from wearing the actigraphy device. If the investigators detect any evidence of development of skin irritation in response to the device, its use will be discontinued.

Safety and Monitoring Plan

As discussed above, every attempt will be made to engage subjects for the duration of the 11-session treatment phase. Subjects will be considered drop-outs from the treatment phase if they fail to attend therapy sessions for three consecutive weeks, in spite of attempts by phone, email and mail to engage the subject in treatment. If at any point during the assessment, treatment or follow-up period, subjects are in need of medical management, psychiatric consultation or psychiatric hospitalization, they will be evaluated and referral or treatment will be provided as indicated. If a subject becomes suicidal, emergency psychiatric assessment will be arranged. The subject will be closely monitored clinically until they are no longer suicidal or an appropriate care plan is in place.

A procedure for clinical deterioration has been established based upon our experience with previous studies. Therapists will be instructed to use their best clinical judgment regarding emergencies and inform the PIs as soon as possible. In addition to relying on clinical judgment on the part of the treating therapists who are experienced with this population, we will also monitor the following weekly: pain, depression, anxiety, substance use, and PTSD symptoms using standardized measures (BPI, BDI, BAI, TLFB, PCL-M, COMM, breathalyzer tests, and urine drug screens) in order to detect any symptom worsening requiring further evaluation. Additionally, subjects will be advised to observe any signs of worsening pain, substance use or depression and to discuss these with their study therapist.

Subjects will be dropped from the study and referred for more intensive treatment if there is: (1) increases in alcohol or drug use leading to the need for a more intensive level of care (i.e., medical detoxification, inpatient or partial hospitalization); (2) active suicidal or homicidal ideation; (3) inability to manage the subject psychiatrically within the inclusion/exclusion criteria of the study (i.e., need for the initiation of psychotropic medications; development of psychosis); or (4) inability to return for therapy appointments due to incarceration or hospitalization.

There is a well-established protocol at our site for emergency psychiatric evaluation, crisis intervention and/or psychiatric hospitalization for suicidal, homicidal, psychotic or other acutely distressed subjects. Immediately on detection of these needs, the assessor/therapist will page a psychiatrist to review the subject's situation. If appropriate, the psychiatrist will personally evaluate the subject. Alternatively, during weekdays, the subject will be escorted by a study staff member to the psychiatric walk-in clinic or emergency room. During evenings or weekends, the site PI or clinical staff will be on-call for emergencies. At these times, acutely distressed subjects will be instructed to go to the psychiatric emergency room for evaluation by the psychiatric resident. The on-call clinical psychologist or psychiatrist will have notified the resident in advance of the subject's situation. Psychiatric hospitalization is available for emergencies.

Suicide Specific Risk Identification and Response Plan

Specific precautions will be taken to prevent harm to subjects and potential subjects. Study therapists will be trained Masters or Doctorate level clinicians and will be supervised by the PI, who is a licensed clinical psychologist. All study therapists and staff will be specifically trained to assess suicide risk, including ideation, plan and intent as well as history of ideation or attempts, and they will be trained to develop a safety contract with subjects. In initial screening procedures, subjects identified by clinical interview with both suicidal ideation and acute intent will be excluded from the study, but will be offered emergency psychiatric care immediately. This care is available 24 hours per day at the Charleston VAMC and MUSC, as indicated above. Moreover, during the course of the study, any subject scoring above 25 on the BDI-II (administered weekly) or answering a 1 or above to question 9 will be specifically queried about suicidal ideation and intent. In any instance where ideation or intent is identified, the PI will be immediately notified and will contact the subject for further evaluation. If both ideation and intent are present, the aforementioned hospital intervention will be provided. Thus, all assessment points represent suicide risk identification, assessment, and intervention opportunities. Study therapists and staff will be specifically trained regarding the increased risk of suicide in Veterans with chronic

pain and substance use disorders, and will receive specific instruction of suicide risk assessment during the initial training workshop.

Informed Consent Procedures

Informed consent will be collected by the on-site Study Coordinator, Research Assistant, PI (Dr. Borckardt), Co-Is (Drs. Brady, McCauley, Barth, Hanlon, Santa Ana or Flanagan), or the VAMC Pain Management Clinic (PMC) Recruitment Liaison (Dr. Goble). The PI and Co-Is are all PhD or MD level clinicians. All study personnel will first be asked to read the treatment protocol and will then attend trainings given by the PI in collaboration with the Co-Is. This is so that each person collecting informed consent is familiar with all aspects of the study. Individuals obtaining informed consent will receive specific additional training by the PI in how to provide study information and obtain consent for study participation and will role-play consent procedures until they demonstrate competency in this area.

Informed consent will be collected at the study research offices, in a private and interruption-free environment. Potential candidates will not be required to make a decision to participate at this initial contact, though that possibility will be available. However, if they wish to discuss participation with their families and/or significant others, or other healthcare providers they will be encouraged to do so.

Protection of Confidentiality / Disposition of Data

We will take careful precautions to maintain confidentiality for all subjects, using procedures we have used with similar previous studies: The investigators and their research assistants (RA) will sign a confidentiality agreement that no identifying information of specific individuals will appear in any internal reports prepared for MUSC or the VA, or external documents (e.g., peer-reviewed publications, presentations). All study data related to psychological outcomes (i.e., the subject responses to questionnaires) and demographics will not have any unique identifying data attached in any way. There will be no linkage between a participant's identity and their responses. There will be only one master list of subjects (again, not linked to any subject responses), which will be destroyed upon study completion; it will be kept separate from all data and will be available only to the PI, Study Coordinator, and RA.

All data will be stored in a confidential manner (i.e., in locked files or on encrypted computers in the Study Coordinator's or RA's research office) so as to protect the confidentiality of subject information. Access to research records will be restricted to the project staff. Specifically, access to de-identified study data will be limited to named project investigators, the Study Coordinator, NIH audit personnel, MUSC IRB audit personnel, and the VAMC Research & Development (R&D) committee personnel. Data will be maintained per an IRB-approved protocol. When study results are published or presented, only aggregate reports of the results will be used and subjects' identity will not be revealed. All analyses will be conducted on de-identified data only.

All investigators and project personnel have completed a certified program of instruction in the protection of human subjects in research, such as the VA website tutorial, NIH website tutorial or the University of Miami CITI course. These courses in the responsible conduct of research and the protection of human research subjects will be completed on an annual basis, in compliance with MUSC institutional and NIH regulations.

Potential Benefits of the Proposed Research

There will be no guarantee of a specific benefit to individual participants; however, the potential benefits include a reduction in aversive symptoms of pain, prescription opioid use severity, and other substance use severity, and improvement in associated mental health problems (e.g., depression, anxiety, sleep). During the study, subjects will learn specific, evidence-based cognitive-behavior techniques to help reduce chronic pain. If they are randomized to a real tDCS group, there is a chance that they will experience less pain than if they had been randomized to a sham group, and that their pain reduction will last longer. Other study benefits include regular contact with research staff, as well as access to assessment information pertaining to mental health, substance abuse, etc. Finally, subjects may benefit from the cognitive realization that, through their study participation, they are helping to advance the state of knowledge as it applies to mental health care for U.S. military personnel and Veterans.

Importance of Knowledge to be Gained

The potential benefits of the knowledge to be gained from the proposed study are considerable. The study has the potential to challenge current paradigms by integrating a new brain stimulation technology during the receipt of more established CBT interventions for chronic pain. The results could improve the way that

clinicians manage a wide variety of chronic pain and co-morbid psychiatric disorders (particularly substance use disorders, depression and PTSD) by utilizing non-pharmacologic neuro-modulation techniques.

The results of this study will provide important information regarding two non-pharmacologic, evidence-based interventions (CBT and tDCS), and will help inform policies and programs to better serve the needs of U.S. military personnel, Veterans, and their families. The proposed study will also help elucidate the mechanisms underlying improved outcomes. The findings from this study may help reduce public health expenditures and morbidity/mortality associated with chronic pain and co-morbid prescription opioid use disorders, improve military readiness, and improve patient care provided in the military healthcare system.

Risk Benefit Ratio

As discussed above, our research team will attempt to maximize potential benefits and minimize potential risks. Knowledge gained by the proposed study will help address the immediate need for empirical evidence regarding optimal, non-pharmacologic treatments for Veterans and their family members with chronic pain and comorbid prescription opioid use disorders. Should new information that would affect the risk-benefit ratio become available during the course of the trial, subjects will be notified and modifications made in consultation with the Data and Safety Monitoring Board (DSMB).

Data and Safety Monitoring (DSM) Plan

This section is based on the recommendations in NIDA's "Guidelines for Developing a Data and Safety Monitoring Plan" (www.drugabuse.gov/funding/dsmbsop.html).

Summary of the Protocol. This application proposes to test the feasibility and preliminary efficacy of tDCS in combination with CBT to improve sleep, and reduce pain and severity of prescription opiate use disorders among Veterans and their family members with chronic pain and co-morbid prescription opioid use disorders. The primary outcome of interest includes reduction in pain and opioid use severity, and improve sleep.

Trial Management. The study will be primarily managed from the Brain Stimulation Lab (Dr. Borckardt, Contact PI) within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina. The target population is described above in the inclusion/exclusion criteria.

Data Management and Analysis. A detailed data analysis plan is outlined in the Statistical Analysis and Power section. Primary outcomes include pain (BPI, daily diary ratings), opioid use severity (COMM, TLFB), and sleep (actigraphy sleep measures). Analyses will be guided by the specific hypotheses of the study. Post-hoc exploratory analyses will be conducted with two-tailed tests and more conservative statistical procedures which guard against Type I error (e.g., Tukey tests). All primary hypotheses will be tested at level of significance $\alpha=0.05$. We will also estimate the effect sizes of interest and provide 95% confidence intervals for them. See the Statistical Analysis and Power section for more details.

Quality Assurance. Data quality will be monitored by random inspection of the completed forms by research staff and any irregularities or problems detected will be discussed with the PI. Study therapists will receive standardized training from the PI and Dr. Otis (Consultant on this project) who develop the CBT intervention to be utilized in the proposed study. Adherence to the manual will be monitored using videotapes and weekly supervision. If therapy drift is observed the therapists will be re-trained. Booster sessions will be held annually.

Regulatory Issues. All unexpected Adverse Events (AEs) will be reported to the MUSC IRB within 10 working days. Serious AEs (SAEs) will be reported within 24-business hours. Follow-up of all unexpected and serious AEs will also be reported to these agencies. All AEs are reviewed weekly by the PI, bi-annually by the Data Safety Monitoring Board (DSMB) and yearly by the IRB. Any significant actions taken by the local IRB and protocol changes will be relayed to NIH. AEs and SAEs occurring during the course of the trial will be collected, documented, and reported in accordance with protocol and IRB reporting requirements. All research staff involved with adverse event reporting will receive general and protocol specific AE/SAE training including identification, assessment and evaluation, and documentation and reporting. The Study Coordinator, Research Assistant or Study Therapists will identify any potential AEs during the course of the study from subject self-report and administration of assessments and procedures. This information will be provided to the Study Physician (Dr. Barth), who will be responsible for AE/SAE assessment and evaluation including a determination of seriousness and study relatedness.

Definition of AE and SAE. Adverse events are defined as any untoward medical occurrence that may present itself during treatment or administration of an intervention, and which may or may not have a causal relationship with the treatment. Serious adverse events are defined as any medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect.
  OR
- Requires intervention to prevent one of the above outcomes.

Documentation and Reporting. AEs/SAEs are documented and reported as per protocol and IRB requirements. Research staff will identify adverse events and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome and the need for change or discontinuation in the study intervention. Adverse events are generally documented on AE Logs and AE Case Report Forms (CRFs). Additional relevant AE information if available should be documented in a progress note in the research record as appropriate to allow monitoring and evaluating of the AE. If the AE meets the definition for serious, appropriate SAE protocol specific reporting forms are completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization or until the subject is no longer in the study as stated in the protocol.

When a reportable SAE is identified, the Study Coordinator will initiate an SAE form, and the following individuals will be notified by facsimile transmission, email and/or telephone within 24-business hours of the initial notification of the SAE:

i. The Principal Investigator and the Study Physician will provide oversight, consultation, assessment and documentation as appropriate of the SAE.

ii. The research staff will notify the MUSC IRB and complete the AE report form in conjunction with the PI. The MUSC IRB meets monthly and is located at 165 Cannon Street, Rm. 501, Charleston, SC 29425. Communication with the IRB is through email, memos, official IRB forms, and online reporting.

iii. The NIH program officer.

iv. The DSMB members.

If complete information is not available when the initial 24-hour SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc. The research staff will attach copies of source documents to the SAE report for review by the PI and for forwarding to the NIH program officer as appropriate within 2 weeks of the initial SAE report. In addition, the PI will provide a signed, dated SAE summary report, which will be sent to the NIH Medical Safety Officer within two weeks of the initial SAE report.

We will report adverse events to the MUSC IRB online as soon as possible, but no later than 10 working days after the investigators first learn of the event. The MUSC IRB AE reporting requirements are as follows: All deaths that occur during the study or 30 days post termination from the study are required to be reported as adverse events even if they are expected or unrelated. Other adverse events are reportable to the MUSC IRB if the AE is unexpected AND related or possibly related AND serious or more prevalent than expected. All three criteria must be met for an AE to be reported to the MUSC IRB. The IRB definition of unexpected is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of related is that there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention. Reportable AEs are reviewed by the IRB Chair and reported to the IRB Board at the next meeting.

Trial Safety. The potential risks and benefits and methods to minimize these risks are outlined above. Protocols for reported AEs and SAEs are outlined above. All unexpected AE and SAEs will be monitored until resolved. A detailed summary of all AEs will be prepared weekly by the research staff. At the weekly

team meetings (or before if urgent), the research staff will report any premonitory symptoms of clinical deterioration.

Study procedures will follow as much as possible the FDA's Good Clinical Practice Guidelines (www.fda.gov/oc/gcp). Any outside requests for information or any breaches in confidentiality will be reported to the PI. All requests by subject's physicians and other medical providers will be referred directly to PI.

DSM Plan Administration. The PI will be responsible for monitoring the study. He will regularly (quarterly) examine the database for missing data, unexpected distributions or responses, and outliers. A DSM report will be filed with the IRB on a yearly basis, unless greater than expected problems occur. The report will include subject characteristics, retention and disposition of study subjects, quality assurance issues and reports of AEs, significant/unexpected AEs and serious AEs. We will report results at the end of the trial.

DSM Board. We will create a DSMB to monitor the overall participant safety, the rate and severity of adverse events, and the validity and integrity of the data. The panel includes 3 researchers with experience in treating patients with chronic pain, substance use disorders, opioid use disorders and/or Veteran populations (Susan Sonne, PharmD; Karen Hartwell, MD; Kelly S. Barth, DO). The board may be called at any point if needed for unexpected AEs, etc. Modification will be made in the procedures and/or the protocol if necessary based on the recommendations of the board.

Confidentiality will be maintained during all phases of the trial including monitoring, preparation of interim results, review, and response to monitoring recommendations.

ClinicalTrials.gov Requirements

In accordance with Public Law 110-85, the proposed trial will be registered with ClinicalTrials.gov. Applicable requirements regarding results reporting will be adhered to.

Inclusion of Women and Minorities

Both male and female subjects will be recruited. There will be no exclusion based on race or ethnicity. Subjects will be recruited without preference for gender, race, ethnicity or socio-economic status. Based on our previous VA data and ongoing RCTs with Veterans, we estimate that approximately 40% of the sample will be comprised of African Americans. We also will include female subjects; however, the percentage of female subjects in our catchment area is low (<8%). Thus, we do not anticipate a large number of female subjects (5%).

Inclusion of Children

The age range for the study is 18-70 years.

Literature Cited

1. Gironda, R.J., M.E. Clark, J.P. Massengale, and R.L. Walker, Pain among veterans of Operations Enduring Freedom and Iraqi Freedom. Pain Med, 2006. 7(4): p. 339-343. pmc-id:
2. Lew, H.L., J.D. Otis, C. Tun, R.D. Kerns, M.E. Clark, and D.X. Cifu, Prevalence of chronic pain, posttraumatic stress disorder, and persistent postconcussive symptoms in OIF/OEF veterans: polytrauma clinical triad. J Rehabil Res Dev, 2009. 46(6): p. 697-702. pmc-id:
3. Macey, T.A., B.J. Morasco, J.P. Duckart, and S.K. Dobscha, Patterns and correlates of prescription opioid use in OEF/OIF veterans with chronic noncancer pain. Pain Med. 12(10): p. 1502-1509. pmc-id: PMC3724513
4. Seal, K.H., Y. Shi, G. Cohen, B.E. Cohen, S. Maguen, E.E. Krebs, et al., Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. JAMA. 307(9): p. 940-947. pmc-id:
5. Manchikanti, L., S. Helm, 2nd, B. Fellows, J.W. Janata, V. Pampati, J.S. Grider, et al., Opioid epidemic in the United States. Pain Physician. 15(3 Suppl): p. ES9-38. pmc-id:
6. Manchikanti, L., S. Abdi, S. Atluri, C.C. Balog, R.M. Benyamin, M.V. Boswell, et al., American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2--guidance. Pain Physician. 15(3 Suppl): p. S67-116. pmc-id:
7. Dobscha, S.K., B.J. Morasco, J.P. Duckart, T. Macey, and R.A. Deyo, Correlates of prescription opioid initiation and long-term opioid use in veterans with persistent pain. Clin J Pain. 29(2): p. 102-108. pmc-id: PMC3531630
8. Gatchel, R.J., Y.B. Peng, M.L. Peters, P.N. Fuchs, and D.C. Turk, The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull, 2007. 133(4): p. 581-624. pmc-id:
9. Henschke, N., R.W. Ostelo, M.W. van Tulder, J.W. Vlaeyen, S. Morley, W.J. Assendelft, et al., Behavioural treatment for chronic low-back pain. Cochrane Database Syst Rev, (7): p. CD002014. pmc-id:
10. Kraaimaat, F.W., M.R. Brons, R. Geenen, and J.W. Bijlsma, The effect of cognitive behavior therapy in patients with rheumatoid arthritis. Behav Res Ther, 1995. 33(5): p. 487-495. pmc-id:
11. Sharpe, L., T. Sensky, N. Timberlake, B. Ryan, C.R. Brewin, and S. Allard, A blind, randomized, controlled trial of cognitive-behavioural intervention for patients with recent onset rheumatoid arthritis: preventing psychological and physical morbidity. Pain, 2001. 89(2-3): p. 275-283. pmc-id:
12. Dixon, K.E., F.J. Keefe, C.D. Scipio, L.M. Perri, and A.P. Abernethy, Psychological interventions for arthritis pain management in adults: a meta-analysis. Health Psychol, 2007. 26(3): p. 241-250. pmc-id:
13. Evers, A.W., F.W. Kraaimaat, P.L. vanRiel, and A.J. deJong, Tailored cognitive-behavioral therapy in early rheumatoid arthritis for patients at risk: a randomized controlled trial. Pain, 2002. 100(1-2): p. 141-153. pmc-id:
14. Gracely, R.H., M.E. Geisser, T. Giesecke, M.A. Grant, F. Petzke, D.A. Williams, et al., Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain, 2004. 127(Pt 4): p. 835-843. pmc-id:
15. Jensen, K.B., E. Kosek, R. Wicksell, M. Kemani, G. Olsson, J.V. Merle, et al., Cognitive Behavioral Therapy increases pain-evoked activation of the prefrontal cortex in patients with fibromyalgia. Pain. 153(7): p. 1495-1503. pmc-id:
16. Li, X., Z. Nahas, F.A. Kozel, B. Anderson, D.E. Bohning, and M.S. George, Acute left prefrontal transcranial magnetic stimulation in depressed patients is associated with immediately increased activity in prefrontal cortical as well as subcortical regions. Biol Psychiatry, 2004. 55(9): p. 882-890. pmc-id:
17. Lorenz, J., S. Minoshima, and K.L. Casey, Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain, 2003. 126(Pt 5): p. 1079-1091. pmc-id:
18. Seminowicz, D.A. and K.D. Davis, Cortical responses to pain in healthy individuals depends on pain catastrophizing. Pain, 2006. 120(3): p. 297-306. pmc-id:
19. Zubieta, J.K., J.A. Bueller, L.R. Jackson, D.J. Scott, Y. Xu, R.A. Koeppe, et al., Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. J Neurosci, 2005. 25(34): p. 7754-7762. pmc-id:
20. Wager, T.D., J.K. Rilling, E.E. Smith, A. Sokolik, K.L. Casey, R.J. Davidson, et al., Placebo-induced changes in FMRI in the anticipation and experience of pain. Science, 2004. 303(5661): p. 1162-1167. pmc-id:

21. Graff-Guerrero, A., J. Gonzalez-Olvera, A. Fresan, D. Gomez-Martin, J.C. Mendez-Nunez, and F. Pellicer, Repetitive transcranial magnetic stimulation of dorsolateral prefrontal cortex increases tolerance to human experimental pain. Brain Res Cogn Brain Res, 2005. 25(1): p. 153-160. pmc-id:
22. Sampson, S.M., J.D. Rome, and T.A. Rummans, Slow-frequency rTMS reduces fibromyalgia pain. Pain Med, 2006. 7(2): p. 115-118. pmc-id:
23. Borckardt, J.J., A.R. Smith, S.T. Reeves, M. Weinstein, F.A. Kozel, Z. Nahas, et al., Fifteen minutes of left prefrontal repetitive transcranial magnetic stimulation acutely increases thermal pain thresholds in healthy adults. Pain Res Manag, 2007. 12(4): p. 287-290. pmc-id: 2670740
24. Akitsuki, Y. and J. Decety, Social context and perceived agency affects empathy for pain: an event-related fMRI investigation. Neuroimage, 2009. 47(2): p. 722-734. pmc-id:
25. Tracey, I., A. Ploghaus, J.S. Gati, S. Clare, S. Smith, R.S. Menon, et al., Imaging attentional modulation of pain in the periaqueductal gray in humans. J Neurosci, 2002. 22(7): p. 2748-2752. pmc-id:
26. Wager, T.D., D.J. Scott, and J.K. Zubieta, Placebo effects on human mu-opioid activity during pain. Proc Natl Acad Sci U S A, 2007. 104(26): p. 11056-11061. pmc-id: 1894566
27. Eippert, F., U. Bingel, E.D. Schoell, J. Yacubian, R. Klinger, J. Lorenz, et al., Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron, 2009. 63(4): p. 533-543. pmc-id:
28. Apkarian, A.V., Y. Sosa, S. Sonty, R.M. Levy, R.N. Harden, T.B. Parrish, et al., Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci, 2004. 24(46): p. 10410-10415. pmc-id:
29. Antal, A., N. Brepohl, C. Poreisz, K. Boros, G. Csifcsak, and W. Paulus, Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. Clin J Pain, 2008. 24(1): p. 56-63. pmc-id:
30. Antal, A., T.Z. Kincses, M.A. Nitsche, and W. Paulus, Manipulation of phosphene thresholds by transcranial direct current stimulation in man. Exp Brain Res, 2003. 150(3): p. 375-378. pmc-id:
31. Antal, A., D. Terney, S. Kuhnl, and W. Paulus, Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. J Pain Symptom Manage. 39(5): p. 890-903. pmc-id:
32. Bachmann, C.G., S. Muschinsky, M.A. Nitsche, R. Rolke, W. Magerl, R.D. Treede, et al., Transcranial direct current stimulation of the motor cortex induces distinct changes in thermal and mechanical sensory percepts. Clin Neurophysiol. pmc-id:
33. Jurgens, T.P., A. Schulte, T. Klein, and A. May, Transcranial direct current stimulation does neither modulate results of a quantitative sensory testing protocol nor ratings of suprathreshold heat stimuli in healthy volunteers. Eur J Pain. 16(9): p. 1251-1263. pmc-id:
34. Borckardt, J.J., M. Bikson, H. Frohman, S.T. Reeves, A. Datta, V. Bansal, et al., A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. J Pain. 13(2): p. 112-120. pmc-id:
35. Nahmias, F., C. Debes, D.C. de Andrade, A. Mhalla, and D. Bouhassira, Diffuse analgesic effects of unilateral repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers. Pain, 2009. 147(1-3): p. 224-232. pmc-id:
36. Rosen, A.C., M. Ramkumar, T. Nguyen, and F. Hoeft, Noninvasive transcranial brain stimulation and pain. Curr Pain Headache Rep, 2009. 13(1): p. 12-17. pmc-id: 2697608
37. Boggio, P.S., S. Zaghi, M. Lopes, and F. Fregni, Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. European journal of neurology : the official journal of the European Federation of Neurological Societies, 2008. 15(10): p. 1124-1130. pmc-id:
38. Borckardt, J.J., A.R. Smith, S.T. Reeves, A. Madan, N. Shelley, R. Branham, et al., A pilot study investigating the effects of fast left prefrontal rTMS on chronic neuropathic pain. Pain Med, 2009. 10(5): p. 840-849. pmc-id:
39. Lefaucheur, J.P., Use of repetitive transcranial magnetic stimulation in pain relief. Expert Rev Neurother, 2008. 8(5): p. 799-808. pmc-id:
40. Arul-Anandam, A.P., C. Loo, D. Martin, and P.B. Mitchell, Chronic neuropathic pain alleviation after transcranial direct current stimulation to the dorsolateral prefrontal cortex. Brain stimulation, 2009. 2(3): p. 149-151. pmc-id:

41. Wagner, T., F. Fregni, and S. Fecteau, Transcranial direct current stimulation: a computer based human model study. Neuroimage, 2007. 35: p. 1113-1124. pmc-id:
42. Wagner, T., A. Valero-Cabre, and A. Pascual-Leone, Noninvasive human brain stimulation. Annu Rev Biomed Eng, 2007. 9: p. 527-565. pmc-id:
43. Wassermann, E.M. and J. Grafman, Recharging cognition with DC brain polarization. Trends Cogn Sci, 2005. 9(11): p. 503-505. pmc-id:
44. Nitsche, M.A. and W. Paulus, Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology, 2001. 57(10): p. 1899-1901. pmc-id:
45. Nitsche, M.A., L.G. Cohen, E.M. Wassermann, A. Priori, N. Lang, A. Antal, et al., Transcranial direct current stimulation: State of the art 2008. Brain Stimul, 2008. 1(3): p. 206-223. pmc-id:
46. Li, X., R.J. Malcolm, K. Huebner, C.A. Hanlon, J.J. Taylor, K.T. Brady, et al., Low frequency repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex transiently increases cue-induced craving for methamphetamine: A preliminary study. Drug Alcohol Depend. pmc-id:
47. Li, X., K.J. Hartwell, M. Owens, T. Lematty, J.J. Borckardt, C.A. Hanlon, et al., Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex reduces nicotine cue craving. Biol Psychiatry. 73(8): p. 714-720. pmc-id: PMC3615051
48. Goldman, R.L., J.J. Borckardt, H.A. Frohman, P.M. O'Neil, A. Madan, L.K. Campbell, et al., Prefrontal cortex transcranial direct current stimulation (tDCS) temporarily reduces food cravings and increases the self-reported ability to resist food in adults with frequent food craving. Appetite. 56(3): p. 741-746. pmc-id:
49. Boggio, P.S., S. Zaghi, and F. Fregni, Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). Neuropsychologia, 2009. 47(1): p. 212-217. pmc-id:
50. Boggio, P.S., S. Zaghi, M. Lopes, and F. Fregni, Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. Eur J Neurol, 2008. 15(10): p. 1124-1130. pmc-id:
51. Salomons, T.V., T. Johnstone, M.M. Backonja, and R.J. Davidson, Perceived controllability modulates the neural response to pain. J Neurosci, 2004. 24(32): p. 7199-7203. pmc-id:
52. Borckardt, J.J., J. Romagnuolo, S.T. Reeves, A. Madan, H. Frohman, W. Beam, et al., Feasibility, safety, and effectiveness of transcranial direct current stimulation for decreasing post-ERCP pain: a randomized, sham-controlled, pilot study. Gastrointest Endosc. 73(6): p. 1158-1164. pmc-id:
53. Borckardt, J., S. Reeves, and M. George, The potential role of brain stimulation in the management of postoperative pain. Journal of Pain Management, 2009. 2(3): p. 295-300. pmc-id:
54. Borckardt, J.J., S.T. Reeves, M. Weinstein, A.R. Smith, N. Shelley, F.A. Kozel, et al., Significant analgesic effects of one session of postoperative left prefrontal cortex repetitive transcranial magnetic stimulation: A replication study. Brain Stimulat, 2008. 1(2): p. 122-127. pmc-id: 2744083
55. Borckardt, J.J., M. Weinstein, S.T. Reeves, F.A. Kozel, Z. Nahas, A.R. Smith, et al., Post-Operative Left Prefrontal Repetitive Transcranial Magnetic Stimulation (rTMS) Reduces Patient-Controlled Analgesia Use Anesthesiology, 2006. 105: p. 557-562. pmc-id:
56. Taylor, J.J., J.J. Borckardt, and M.S. George, Endogenous opioids mediate left dorsolateral prefrontal cortex rTMS-induced analgesia. Pain, 2012. pmc-id:
57. Hanlon, C.A., M. Canterberry, J.J. Taylor, W. DeVries, X. Li, T.R. Brown, et al., Probing the frontostriatal loops involved in executive and limbic processing via interleaved TMS and functional MRI at two prefrontal locations: a pilot study. PLoS One. 8(7): p. e67917. pmc-id: PMC3706588
58. Back, S.E., Toward an improved model of treating co-occurring PTSD and substance use disorders. Am J Psychiatry. 167(1): p. 11-13. pmc-id: PMC2859044
59. Back, S.E., T. Killeen, E.B. Foa, E.J. Santa Ana, D.F. Gros, and K.T. Brady, Use of an integrated therapy with prolonged exposure to treat PTSD and comorbid alcohol dependence in an Iraq veteran. Am J Psychiatry. 169(7): p. 688-691. pmc-id: PMC3654811
60. Back, S., T. Kileen, A. Teer, E. Hartwell, A. Federline, F. Beylotte, et al., Substance use disorders and PTSD: An exploratory study of treatment preferences among military Veterans. Addictive Behaviors, in press. pmc-id:
61. Back, S., E. Foa, T. Kileen, K. Mills, M. Teeson, K. Carroll, et al., Concurrent Treatment of PTSD and Substance Use Disorders using Prolonged Exposure (COPE). Therapist Manual, Oxford University Press, in press. pmc-id:

62. Barth, K.S., M.M. Maria, K. Lawson, S. Shaftman, K.T. Brady, and S.E. Back, Pain and motives for use among non-treatment seeking individuals with prescription opioid dependence. Am J Addict. 22(5): p. 486-491. pmc-id: PMC3748383
63. Back, S.E., R.L. Payne, A.H. Wahlquist, R.E. Carter, Z. Stroud, L. Haynes, et al., Comparative profiles of men and women with opioid dependence: results from a national multisite effectiveness trial. Am J Drug Alcohol Abuse. 37(5): p. 313-323. pmc-id: PMC3164783
64. Gros, D.F., M.E. Milanak, K.T. Brady, and S.E. Back, Frequency and severity of comorbid mood and anxiety disorders in prescription opioid dependence. Am J Addict. 22(3): p. 261-265. pmc-id:
65. Lawson, K.M., S.E. Back, K.J. Hartwell, M. Moran-Santa Maria, and K.T. Brady, A comparison of trauma profiles among individuals with prescription opioid, nicotine, or cocaine dependence. Am J Addict. 22(2): p. 127-131. pmc-id: PMC3681508
66. McGrath, P.J., G.A. Walco, D.C. Turk, R.H. Dworkin, M.T. Brown, K. Davidson, et al., Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. J Pain, 2008. 9(9): p. 771-783. pmc-id:
67. Dworkin, R.H., D.C. Turk, J.T. Farrar, J.A. Haythornthwaite, M.P. Jensen, N.P. Katz, et al., Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain, 2005. 113(1-2): p. 9-19. pmc-id:
68. Meltzer, E.C., D. Rybin, R. Saitz, J.H. Samet, S.L. Schwartz, S.F. Butler, et al., Identifying prescription opioid use disorder in primary care: diagnostic characteristics of the Current Opioid Misuse Measure (COMM). Pain. 152(2): p. 397-402. pmc-id: PMC3027065
69. Butler, S.F., S.H. Budman, G.J. Fanciullo, and R.N. Jamison, Cross validation of the current opioid misuse measure to monitor chronic pain patients on opioid therapy. Clin J Pain. 26(9): p. 770-776. pmc-id: PMC2955853
70. Sobell, L.C., T. Toneatto, M.B. Sobell, G.I. Leo, and L. Johnson, Alcohol abusers' perceptions of the accuracy of their self-reports of drinking: implications for treatment. Addict Behav, 1992. 17(5): p. 507-511. pmc-id:
71. Carey, K.B., Challenges in assessing substance use patterns in persons with comorbid mental and addictive disorders. NIDA Res Monogr, 1997. 172: p. 16-32. pmc-id:
72. Otis, J.D., T.M. Keane, R.D. Kerns, C. Monson, and E. Scioli, The development of an integrated treatment for veterans with comorbid chronic pain and posttraumatic stress disorder. Pain Med, 2009. 10(7): p. 1300-1311. pmc-id:
73. DeRubeis, R.J., S.D. Hollon, M.D. Evans, and K.M. Bemis, Can psychotherapies for depression be discriminated? A systematic investigation of cognitive therapy and interpersonal therapy. J Consult Clin Psychol, 1982. 50(5): p. 744-756. pmc-id:
74. Roderick, J.A.L., A Test of Missing Completely at Random for Multivariate Data with Missing Values. Journal of the American Statistical Association, 1998. 83(404): p. 1198-1202. pmc-id:
75. Bramoweth, A.D., J.G. Renqvist, A. Germain, D.J. Buysse, A. Gentili, G. Kochersberger, et al., Deconstructing Chronic Low Back Pain in the Older Adult-Step by Step Evidence and Expert-Based Recommendations for Evaluation and Treatment: Part VII: Insomnia. Pain Med, 2016. 17(5): p. 851-863. pmc-id:
76. Paanalahti, K., M.M. Wertli, U. Held, T. Akerstedt, L.W. Holm, M. Nordin, et al., Spinal pain-good sleep matters: a secondary analysis of a randomized controlled trial. Eur Spine J, 2016. 25(3): p. 760-765. pmc-id:
77. Roizenblatt, S., A.L. Souza, L. Palombini, L.M. Godoy, S. Tufik, and L.R. Bittencourt, Musculoskeletal Pain as a Marker of Health Quality. Findings from the Epidemiological Sleep Study among the Adult Population of Sao Paulo City. PLoS One, 2015. 10(11): p. e0142726. pmc-id: PMC4657923
78. Shmagel, A., R. Foley, and H. Ibrahim, Epidemiology of chronic low back pain in US adults: National Health and Nutrition Examination Survey 2009-2010. Arthritis Care Res (Hoboken), 2016. pmc-id:
79. Myoji, Y., K. Fujita, M. Mawatari, and Y. Tabuchi, Changes in sleep-wake rhythms, subjective sleep quality and pain among patients undergoing total hip arthroplasty. Int J Nurs Pract, 2015. 21(6): p. 764-770. pmc-id: