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Protocol

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Study Title: **Dose-dependent Effects of tDCS on Post Surgical Pain**

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A. SPECIFIC AIMS

The proper control of acute and chronic pain is one of the most important areas in health care. Despite the profound advances in neuroscience over the past 20 years, we still largely use opiate narcotics, much as was done in the Civil War. Total knee arthroplasty (TKA) is one of the most common orthopedic procedures performed [1]. Because the prevalence of arthritis is expected to grow substantially as the population ages [2 3], these procedures are likely to become even more common. Previous reports suggest that TKA improves functional status, and relieves pain in most patients, and the number and the rate of total knee arthroplasties is increasing steadily. While knee pain is often a complaint that precedes TKA, the procedure itself is associated with considerable post-operative pain lasting days to weeks. Adequate postoperative pain control is an important factor in determining recovery time and hospital length of stay [4 5 6]. While the technology associated with the TKA procedures themselves has developed rapidly in the past several years, post-operative pain management techniques have not changed substantially in several decades. Primary methods used to manage post-operative pain typically involve systemic opioid or other analgesic drug delivery, and regional blocks. Despite these pain-management strategies, patients still report considerable post-operative pain, and often struggle to complete post-operative physical therapy regimens. Additionally, systemic opioid analgesic use, has associated side-effects that can lead to post-operative complications including but not limited to mental-clouding, confusion, respiratory depression, interactions with other medications, addiction in some cases, fatigue, and gastric motility problems. Further, the TKA procedures along with the associated intraoperative anesthesia protocols have been associated with increased risk for post-operative cognitive problems[7] especially among the elderly[8], and current post-operative pain management strategies can exacerbate these problems. For obese TKA patients, apnea is a real concern that systemic opioid use can complicate. These are relevant concerns as the population receiving TKA are more and more likely to be elderly and/or overweight[8, 9]. New analgesic strategies are needed that can be used adjunctively to existing strategies with the potential to reduce reliance on opioid analgesia. Several novel brain stimulation technologies including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are beginning to demonstrate promise as treatments for a variety of pain conditions [10 11 12 13 14, 15]. Electricity has no metabolite or other residue, and can be delivered with minimal discomfort and without problems associated with drug-drug interactions. TMS and tDCS are minimally-invasive and appear effective in the management of chronic pain and experimentally-induced pain[10, 11, 16-30]. Recently, the PI on this proposal found that high frequency TMS for 20-minutes post gastric bypass surgery was associated with approximately

40% less patient-controlled opioid analgesia use than controls during the 48-hour post-operative period, with lower pain ratings[26, 27, 30]. This series of studies was the first to demonstrate the potential of brain stimulation technology to be part of a standard post-operative pain-management strategy, however TMS is more complicated to deliver than tDCS, has more adverse events, and is more cumbersome in the post-operative setting. In two independent preliminary pilot studies, the PI has shown that tDCS can reduce post-operative PCA use by as much as 46% while simultaneously reducing subjective pain ratings. Thus, a handful of preliminary studies have demonstrated the potential for brain stimulation techniques to adjunctively manage post-operative pain, but a more definitive trial is needed to evaluate the efficacy of tDCS using a more rigorous experimental design. Further more data is needed to determine optimal tDCS dosing parameters before tDCS will become a viable clinical intervention for post-operative pain across surgical specialties.

Aim-1: Determine the effects of transcranial direct current stimulation (tDCS) on post-operative pain, patient-controlled analgesia (PCA) use, and post-surgical complications during the 48-hour post-operative period following total knee arthroplasty (TKA)or total hip arthroplasty (THA).

> *Hypothesis 1:* Real tDCS (over sensory/motor and dorsolateral prefrontal cortices) will be associated with decreased PCA morphine-equivalent usage (primary outcome), decreased pain ratings (secondary outcome), and decreased post-operative complications compared to sham tDCS.

Aim-2: Collect preliminary data regarding dose-dependent effects of tDCS on post-operative pain, PCA morphine-equivalent usage, and 6-month outcomes.

> *Hypothesis 2a:* The analgesic benefits of tDCS will be dose dependent such that one 20-minute post-operative tDCS session will be superior to sham, two sessions will be superior to one session, and four sessions will produce the largest analgesic effects in the present study.
>
> *Hypothesis 2b:* Patients receiving higher doses of real tDCS will evidence lower incidence (and dose) of 6-month opioid medication use, reduced pain, and better quality of life.

B. BACKGROUND AND SIGNIFICANCE

Total knee arthroplasty (TKA) is one of the most common orthopedic procedures, and in 2001 171,335 primary knee replacements and 16,895 revisions were performed[1]. Because the prevalence of arthritis is expected to grow substantially as the population ages[2 3], TKA procedures are likely to become even more common. The rate of revision total knee arthroplasties is increasing by approximately 6 procedures per 100,000 persons per decade. TKA has been shown to improve functional status, and relieve pain in many patients. Between 1990 and 2002, the rate of primary total knee arthroplasties per 100,000 persons almost tripled. While knee pain is often a complaint that precedes TKA, the procedure itself is associated with considerable post-operative pain lasting days to weeks post-operatively, and adequate postoperative pain control is an important factor in determining recovery time, hospital length of stay, and long-term surgical outcomes [4 5 6]

Postoperative pain control: Opioid medications are the most powerful and effective drugs for pain relief, however there are risks and problems associated with opioid use [31]. Among the risks are the numerous potential side-effects including: respiratory depression, nausea and vomiting, addiction, cough suppression, mental clouding, sedation, itching of the skin and nose, and constipation. Many of the side-effects of opioid medications are particularly problematic in elderly and obese patients. Thus, new interventions that have the potential to reduce reliance on postoperative opioids in this patient

population (such as TMS and tDCS; see Preliminary Studies) need to be explored.

Recently, Alam et al[32] evaluated the incidence of long- term analgesic use after low-risk surgery in adults not previously prescribed analgesics by conducting a retrospective cohort study using linked, population-based data in Ontario, Canada, from April 1, 1997, through December 31, 2008. Patients were identified that were dispensed an opioid within 7 days of a short-stay, minor surgery and the risk of long-term opioid use was assessed, defined as a prescription for an opioid within 60 days of the 1-year anniversary of the surgery. Among 391,139 opioid-naive patients undergoing short-stay surgery, opioids were newly prescribed to 7.1%. At 1 year from surgery, an increase in the use of oxycodone was found (from 5.4% within 7 days of surgery to 15.9% at 1 year). Patients receiving any opioid prescription within 7 days of surgery were 44% more likely to become long-term opioid users within 1 year compared with those who received no such prescription. Prescription of opioid analgesics immediately after surgery occurs frequently in adults and is associated with long-term use. Thus, post-surgical opioid use appears to be a potential contributing factor to rising incidence and risk of long-term opioid use, dependence and abuse. Patient-controlled analgesia (PCA) pumps have been shown to be very effective in the management of postoperative pain. While the risk of PCA pump usage specifically and directly leading to future opioid abuse is relatively small (1% [33]), opioid abuse appears to be on the rise in the United States [34]. In many cases, both patients and physicians worry about the potential for dependence and abuse of opioid medications, and this sometimes results in under-treatment of acute and chronic pain [33].

Several non-pharmacological approaches to modulating pain perception have been used successfully in postoperative populations. There is accumulating evidence that cognitive, relaxation, and hypnotic interventions can significantly reduce postoperative pain and recovery time [35 36 37 38 39 40 41, 42]. While the mechanisms of action of such approaches are unclear, there is some evidence suggesting that cognitive, relaxation and hypnotic interventions may increase activation of the prefrontal cortex and networks involved in inhibiting the affective dimension of pain experience [43 44]. Unfortunately, these psychological approaches are resource dependent, requiring much time and highly skilled personnel. They are thus unlikely to be widely used in non-research settings. Since tDCS appears to be capable of focally exciting targeted cortical areas involved with central pain processing, and given our preliminary data suggesting significant postoperative pain reduction and decreased morphine use, further exploration of its potential applications in a balanced analgesic approach are warranted. A reasonable strategy for developing optimal balanced analgesia involves first studying optimal treatment combinations for individual procedures [35]. Given the preliminary nature of our understanding of optimal management strategies for postoperative pain across the vast array of available surgical procedures, and given our preliminary findings of the potential effectiveness of tDCS in the management of post-operative pain (see preliminary studies section), it is prudent to ensure that the effect is real and to explore key basic parameters that may be related to optimizing it before expanding the procedure into managing pain from other surgical procedures. We have therefore chosen to use this study to extend and refine the technique using total knee arthroplasty (a group with which the investigative team has extensive experience), rather than to prematurely begin testing whether the effects generalize to other surgical populations.

Pain and the Brain: Pain is a complex experience that has sensory-discriminatory, motivational-affective and cognitive-evaluative dimensions [45]. Experimental and clinical fMRI findings suggest that parietal areas, including the primary somatosensory cortex, are mainly involved in the sensory-discriminative dimension of pain experience and frontolimbic networks are involved in the affective dimension [46 47]. There is also evidence that the primary (SI) and secondary (SII) somatosensory cortices are involved in the temporal processing of pain experience. However, activation of SI tends to be limited to activation contralateral to the side of stimulation, whereas SII tends to demonstrate bilateral activation [47 48 49]. When pain-relevant anxiety is manipulated experimentally, evidence emerges supporting the involvement of the anterior cingulate cortex (ACC) in the affective dimension of pain

experience [46 50]. Innocuous thermal stimulation is associated with activation of the anterior ACC whereas noxious stimulation is associated with activation of both the anterior ACC and the ventral portion of the posterior ACC [51]. Other brain structures that appear to be involved in the affective component of pain experience include the lateral and medial thalamus, insular cortex, and the supplementary motor area [52 53]. There is some evidence supporting the notion that brain structures involved in processing the affective component of pain experience are activated bilaterally whereas structures involved in processing sensory-discriminative components demonstrate unilateral activation [54 55]. The role of the left prefrontal cortex in pain control is unclear. However, there is evidence to support the concept that left prefrontal activation is negatively correlated with pain unpleasantness [56] suggesting a possible governing role of the prefrontal cortex on the affective dimension of pain experience. In fact, it has been shown that prefrontal activation is negatively correlated with pain catastrophizing [57]. This is important as catastrophizing and pain-related anxiety have been identified as a reliable predictor of the development of chronic post-surgical pain. [58] Additionally, recent studies of expectancy and cognitively-mediated analgesia seem to suggest that cognitive effects on pain perception may involve genuine analgesia that is mediated by μ-opioid systems in the brain [59] and are associated with decreased activation of the thalamus, insula and anterior cingulate. These effects correlate with prefrontal cortex activation (where expectations, thoughts and belief-systems are believed to primarily operate in the brain [60]). Thus, left prefrontal activation might result in similar analgesic effects, presumably by modulating limbic response to pain. Interestingly, there appears to be distinct laterality effects regarding dorsolateral prefrontal cortices. Activation of the left DLPFC but deactivation of the right DLPFC tends to be associated with pain inhibition (as well as improvements in mood). [56, 57, 60].

Minimally-invasive brain stimulation technology: Transcranial direct current stimulation (tDCS), involves the application of low-amplitude electric current to the scalp. A battery-powered current generator (capable of delivering up to 2 mA of constant current flow) is attached to two sponge electrodes. The sponge electrodes are then soaked in saline, applied to the scalp, and held in place by a non-conducting rubber montage. During tDCS, low amplitude direct currents penetrate the skull to enter the brain. Although there is substantial shunting of current at the scalp, sufficient current penetrates the brain to modify the transmembrane neuronal potential [74, 75 76] and, thus, influence the level of excitability and modulate the firing rate of individual neurons. Unlike TMS, direct current does not directly induce action potentials, but rather, the current appears to modulate the spontaneous neuronal activity in a polarity-dependent fashion. Anodal tDCS applied over the cortex increases the excitability of the stimulated brain area, while cathodal tDCS applied over the same area decreases it [71 77 78]. Anodal tDCS applied over the occipital cortex produces short-lasting increases in visual cortex excitability [79 80]. Hence, tDCS is believed to deliver its effects by polarizing brain tissue, and while anodal stimulation generally increases excitability and cathodal stimulation generally reduces excitability, the direction of polarization depends somewhat on the orientation of axons and dendrites in the induced electrical field.

Minimally-invasive brain stimulation and pain perception: The first controlled laboratory study of motor tDCS was performed in only 8 healthy subjects who underwent quantitative sensory testing before and after cathodal, anodal, and sham tDCS sessions, performed in a random order [95]. The active electrode was placed over the left M1 and the reference electrode above the right orbit. Cathodal tDCS lowered cold detection threshold, corresponding to a reduced sensitivity to A∂-fiber-mediated somatosensory inputs. No other change was observed. However, this result was not confirmed in a subsequent study with the same design but a larger series of subjects [96].

A third tDCS study was characterized by the use of a unqiue tDCS design, called high-definition tDCS (HD-tDCS; see preliminary studies section) [97]. With this method, 4 cathodes are placed equidistant (7 cm) from each other and from the anode, which serves as the active electrode. This montage increases the spatial selectivity of the stimulation. Anodal HD-tDCS delivered to the left M1

decreased cold detection and pain thresholds, and increased warm sensory thresholds, but did not alter heat pain thresholds. This antinociceptive effect of anodal HD-tDCS runs counter the absence of effect of anodal tDCS in the other studies performed in healthy subjects[95, 96], but fits well with the proved analgesic effect of anodal (but not of cathodal) tDCS in chronic pain, of either neuropathic or non-neuropathic origin [21, 79, 91]. This observation could illustrate the respective influence of disease-related homeoplastic cortical plasticity and stimulation polarity on tDCS efficacy. In general, anodal tDCS tends to reproduce the main effect of high-frequency rTMS that is a decreased sensitivity to cold stimuli and a reduced susceptibility to cold pain. It is generally accepted that cortical excitability is reduced by cathodal tDCS and increased by anodal tDCS because of induced processes of axonal hyperpolarization and depolarization, respectively [78]. Because high-frequency rTMS is thought to increase cortical excitability, the similarity between the effects of high-frequency rTMS and those of anodal tDCS on thermal sensation seems logical. Both methods likely activate some cortical neural circuits running through the precentral gyrus and involved in cold sensation processing. However, this simple approximation should be viewed with caution because, as mentioned above, it is difficult to take the effect on motor corticospinal output as a general rule of action of a type of cortical stimulation. In addition, even if anodal stimulation is exciting and cathodal stimulation is inhibiting, the efficacy of the stimulation may depend partly on the orientation of the axons in the induced electrical field. Moreover, the site of induced biological effects is thought to locate under the active electrode because it is assumed that the other electrode is a reference. This assumption is probably wrong if we consider that in most of tDCS studies, the reference electrode is placed at the forehead or over the orbit, and thus quite close to the orbitofrontal cortex. In these cases, what is interpreted as the effect of anodal stimulation of M1 may be the effect of cathodal stimulation of orbitofrontal cortex.

Stimulation of the primary motor cortex (M1) and dorsolateral prefrontal cortex (DLFPC) may both reduce the perception of pain, but they likely do so via different mechanisms. In a recent study, pain thresholds to electrical stimulation were assessed in 20 healthy volunteers before and during anodal tDCS. Four conditions of stimulation were compared: M1, DLPFC, occipital cortex, and sham. Anodal tDCS of M1 increased both detection and pain thresholds, while stimulation of DLPFC increased pain thresholds only. The results suggested that 1) anodal stimulation of M1 but not DLPFC could induce analgesia by modulating sensory discrimination and 2) stimulation of DLPFC could modulate the perception of pain via mechanisms independent of sensory perception [19]. An adjunctive study with 22 healthy volunteers showed that anodal tDCS of the DLPFC (but not M1, occipital, or sham) could decrease the perception of unpleasantness and reduces emotional discomfort/pain while subjects viewed emotionally aversive images [20].

Overall, we have accumulated considerable knowledge over the past few decades about the relationships between acute/post-surgical pain, pain management strategies, opiate addiction risks, and brain responses to painful stimuli. Additionally, several new brain stimulation technologies have been introduced and tested, and when combined in a thoughtful way with our growing knowledge of pain processing in the brain, there is considerable evidence supporting their potential role in current pain management strategies. Much less attention has been paid to integrating brain stimulation technology into the post-operative setting which is unfortunate given the limits of currently available post-operative pain-management resources, the risks associated with current pain management strategies, and the sky-rocketing increase in opiate addiction in the US. The present study builds on accumulating knowledge about pain processing in the brain and clinical efficacy data supporting brain stimulation for pain. This study will be the first randomized, double-blind, controlled dosing study of tDCS technology as an adjunctive pain management strategy for post-operative pain. Data from this trial will likely yield information regarding the feasibility and efficacy of tDCS as a post-operative pain-management approach. If the proposed pilot trial suggests significant and meaningful effects of tDCS as an adjunctive post-operative pain management strategy, this might change the way post-operative pain management is approached in the future. Findings from this study will be used to evaluate the

necessity for an even larger-scale, multi-site clinical trial of the technique, and to determine whether future investigations of tDCS across different surgical specialties might be warranted.

C. PRELIMINARY STUDIES

Motor Cortex tDCS Laboratory Pain Pilot: Twenty-four healthy, medication-free, adult volunteers (18 female; 6 male; 3 African American; 1 Asian; 20 Caucasian) with a mean age of 26.58 (SD=6.11; range 19 to 43) provided written informed consent to participate in this pilot. Participants did not have depression, chronic pain, epilepsy, seizure-history, or implanted medical devices. Two participants were nicotine dependent smokers. Quantitative Sensory Testing (QST) was conducted using the ATS thermode of the Medoc Pathway system (Medoc Advanced Medical Systems Ltd, NC, USA) attached to the left volar forearm of each subject's left arm ~5 cm from the wrist. The thermode heated or cooled (randomly-ordered) from 32ºC at the rate of 0.25ºC per second. Participants pressed a button to stop the thermode as soon as they detected any change in temperature (sensory threshold), when it reached the level considered to be painful (pain threshold), and when they could no longer tolerate the stimulus (pain tolerance). After 10 trials, the CHEPS thermode from the Medoc Pathway System was used to deliver 20 brief (0.75s) suprathreshold thermal stimuli (individual heat pain threshold plus 1.5ºC) to the left volar forearm of subjects at the rate of 1 stimulus every 1.5 seconds. During the 30-seconds of repeated stimulation, subjects continuously indicated their level of pain intensity using a dynamic computerized visual analogue scale (CVAS) controlled by the mouse. The CVAS recorded the position of the digital marker on the VAS each second. The mean of the pain ratings during the first 3-seconds and the last 3-seconds of the 30-second wind-up trial were examined to determine the amount of wind-up pain experienced by each participant.

The tDCS device was a Phoresor-II Auto (Model PM850, Iomed, Salt Lake City Utah, USA). Participants were randomized to receive real or sham tDCS. For real tDCS, the device was ramped to 2 mA and maintained this current for 20 minutes. For sham tDCS, the device was ramped to 2 mA, but after 30 seconds, was ramped back down to 0 mA and stayed off for the remainder of the 20 minutes. During stimulation, participants rated the painfulness and unpleasantness of any scalp sensations using numeric rating scales (e.g., 0=no pain to 10=worst pain imaginable). Ratings were collected at stimulation onset, 5-minutes, 10-minutes, 15-minutes, and during the last 30-seconds of stimulation). Further, verbal descriptors of all scalp sensations, pain-related or otherwise, were recorded as well as all adverse events associated with the study. At the end of the study, participants were asked to guess whether they received real or sham tDCS. Further, they were asked to rate their confidence in their guess (0=completely guessing to 10=absolutely sure).

Participants rated the scalp pain associated with real tDCS as 1.98 (SD=2.02) out of 10 on average while those receiving sham tDCS rated their scalp pain as 0.18 (SD=0.27). These means are both low considering the 11-point range of the NRS, but they were significantly different ($t(22)=2.94$, $p=.008$). Participants receiving real tDCS rated the unpleasantness of the scalp sensations as 3.34 (SD=2.44) out of 10 on average whereas those receiving sham rated the unpleasantness as 0.43 (SD=0.49) on average ($t(22)=3.88$, $p=.001$). The scalp painfulness and unpleasantness ratings associated with real tDCS decreased over time during stimulation. Despite the between group differences in stimulation painfulness and unpleasantness, participants were not able to correctly guess whether they received real or sham stimulation at a rate better than chance ($X^2(1)=2.10$, $p=.21$, ns). In the real stimulation group, 46% of participants guessed correctly ($X^2=.004$, $p=.94$, ns) and in the sham group 18% guessed correctly ($X^2(1)=2.23$, $p=.14$, ns). The average guess-confidence rating was 5.50 (SD=3.10) in the real tDCS group and 4.55 (SD=2.16) in the sham group ($t(22)=0.86$, $p=.399$, ns).

Qualitative descriptors of the scalp sensations during tDCS included "itchiness" (21% of total sample), "tingling" (21%), "prickling" (13%), "pressure", "stinging", "uncomfortable", and "warm" (8% each). A total of 37 qualitative descriptors were offered by participants in the real tDCS group and 17 from those in the sham group. Those offered by participants in the sham group were primarily during the 30 seconds of stimulation delivered before ramping the device back down to 0mA for the remainder of the 20-minute session. There were no adverse events, and no report of any post-stimulation side-effects.

Sensory Thresholds: There was a significant main effect for time (pre- to post- stimulation; $F(1,166)=148.77$, $p<.0001$) but no main effect for condition (real vs sham stimulation; $F(1,26.4)=0.04$, $p=.85$, ns) on heat sensory thresholds. The procedural pain covariate was not significant ($F(1,21=4.16$, ns). However the time X condition interaction was significant ($F(1,166)=5.34$, $p=.02$). Participants in the real stimulation group evidenced a 0.54ºC increase (estimated marginal mean after controlling for procedural painfulness) in heat sensory threshold pre- to post- stimulation, relative to the sham group. For cold sensory thresholds, there was also a significant main effect for time ($F(1,165)=50.82$, $p<.0001$) but not for condition ($F(1,29)=1.64$, $p=.21$, ns), but the time X condition interaction term was significant ($F(1,165)=7.74$, $p=.006$). The procedural pain covariate was not significant ($F(1,21)=3.17$, ns). Participants in the real stimulation group evidenced a 0.76ºC decrease (estimated marginal mean after controlling for procedural painfulness) in cold sensory threshold pre- to post- stimulation relative to sham.

Thermal Pain Thresholds: A main effect for time was observed on heat pain thresholds ($F(1,260)=64.94$, $p<.0001$), but no main effect was found for condition or for the time X condition interaction term ($F(1,22.8)=0.48$, $p=.49$, ns; $F(1,260)=0.19$, $p=.66$, ns). The procedural pain covariate was not significant ($F(1,21)=0.21$, ns). For cold pain thresholds, a significant main effect was found for time ($F(259)=4.55$, $p=.03$) but not condition ($F(1,22.1)=2.82$, $p=.11$, ns). Only a marginal effect was observed for the time X condition interaction term ($F(1,259)=3.18$, $p=.07$). The procedural pain covariate was not significant ($F(1,21)=0.85$, ns). Participants that received real stimulation evidenced a 0.82ºC decrease (estimated marginal mean after controlling for procedural painfulness) in cold pain threshold relative to sham.

Thermal Wind-up Pain: A significant time (pre- to post- stimulation) X condition (real versus sham stimulation) X wind-up pain slope interaction was observed ($F(4,44)=5.43$, $p=.001$). For those receiving real stimulation, the wind-up pain slope decreased by 0.25 CVAS pain-rating points-per-second (during the 30-second wind-up trial) following stimulation relative to baseline ($t(21.8)=2.21$, $p=.036$). However, in the sham stimulation group, there was no change in wind-up pain slope pre- to post- stimulation ($t(30)=0.52$, $p=.61$, ns).

In our recent laboratory pilot, real tDCS was associated with significantly decreased heat and cold sensory thresholds, decreased thermal wind-up pain, and a marginal analgesic effect for cold pain thresholds, all after controlling for procedural painfulness ratings. No significant effects were observed for heat pain thresholds. Similar studies using TMS suggest that stimulation of the motor cortex is associated with changes in heat and cold sensory thresholds as well as heat and cold pain thresholds [89, 98, 99]. Using tDCS, Bachmann et al [95] found that cathodal stimulation over the motor cortex significantly impacted cold sensory, mechanical sensory and mechanical pain thresholds in the contralateral hand. Bachmann et al found no significant effects for cold pain thresholds, pressure pain thresholds or wind-up pain. The simplest explanation for the divergence between these findings and those from the present study, is the significant difference in the spatial profile of induced brain current flow. Craig et al found that the application of innocuous cold stimuli activates the human thermosensory cortex located in the contralateral insula [100]. Painful heat and cold stimuli activated the contralateral anterior cingulate cortex (ACC), contralateral primary motor and sensory cortex (MI: primary motor cortex/SI: primary sensory cortex), bilateral secondary sensory cortex (SII: secondary sensory cortex)

and mid-insular cortex, thalamus, and the vermis and paravermis of the cerebellum [101] [64]. Thus, the differing effects of tDCS and TMS seen on laboratory pain measures and non-painful thermal and nociceptive thermal signals may be due, in part, to the transmission of signals related to perception via these different stimulus types may occur through unique pathways.[95] In addition, tDCS modulation of innocuous thermal thresholds may be more easily achieved than modulation of thermal pain thresholds, as thermal perception and distinction thresholds are lower than thermal pain thresholds. [95]

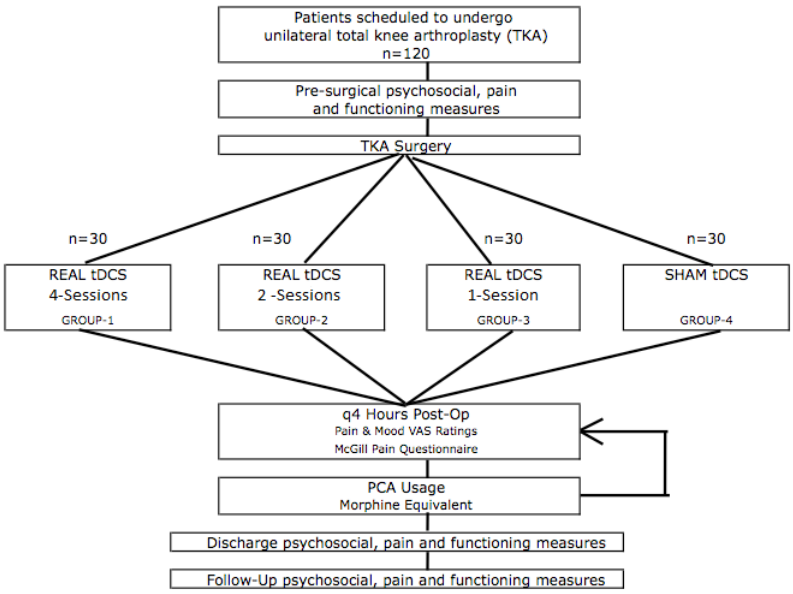
tDCS Effects on Post-Procedural Pain Pilot: [102] Recently, the PI conducted the first-ever pilot study on the effects of tDCS on post- Endoscopic Retrograde Cholangiopancreatography (ERCP) pain. Nineteen Caucasian females (mean age=37.2 StdErr=2.4) were enrolled. After ERCP, participants were randomly assigned to receive 20-minutes of tDCS with anode over the left-prefrontal cortex and cathode over the gut representation of the sensory cortex. No serious adverse events were associated with tDCS. Side-effects of tDCS were limited to tingling (42%), itching (47%) and mild stinging (11%) under the electrodes. Patients that received a single 20-minute dose of real tDCS used 22% less total hydromorphone than those that received sham at the end of the 24-hour inpatient post-procedural period (Cohen's d=.38). The slope of the cumulative PCA usage curve was significantly steeper in the sham tDCS group compared to real ($t(355)=10.80$, $p<.0001$). VAS pain scores suggested an arithmetic advantage for real tDCS compared to sham (not statistically significant likely due to limited power). *Results from this pilot feasibility study suggest that tDCS is safe, well-tolerated, and may be able to reduce post-ERCP opioid requirements without increasing subjective pain ratings.*

tDCS Effects on Post-Total-Knee-Arthroplasty (TKA) Pain Pilot: In a very recent preliminary pilot study, the PI randomly assigned 40 patients undergoing unilateral TKA to receive a total of 80 minutes of real (n=20) or sham tDCS (n=20) with the anode over the knee representation of the motor strip and cathode over the right dorsolateral prefrontal cortex. 20-minute tDCS treatments were delivered: 1) in the PACU, 2) 4 hours later, 3) the morning of post-operative day-1, and 4) the afternoon of post-operative day-1. VAS pain and mood ratings were collected every 4 hours following surgery provided that patients were awake. The slopes of the cumulative PCA usage curves were significantly different between groups, and those TKA in the real tDCS group used 44% less PCA dilaudid at 48-hours post-op ($p=.007$; Cohen's $d=1.0$). Despite significantly lower PCA dilaudid levels, VAS ratings of pain-on-average were also significantly lower in the real tDCS group ($t(37)=2.28$, $p=.029$). No adverse events or serious adverse events were encountered. There were no cases in which tDCS needed to be discontinued due to patient discomfort or tDCS-related complications.

Overall, we have found that stimulating pain-modulating areas of the human cortex can significantly reduce post-operative opioid requirements without negatively impacting subjective pain ratings, and in some cases, it can significantly decrease pain ratings even though patients use less opioids. Further, we observe large effect-sizes for 20-minutes of TMS and for 80-minutes of tDCS. The investigators have demonstrated the feasibility of, and expertise for conducting brain stimulation in the post-operative setting and these promising, preliminary findings of novel brain stimulation technologies suggest that future studies are warranted. The field of minimally-invasive brain stimulation for pain is expanding rapidly, but it is still in its infancy. tDCS appears to have the potential to serve as an adjunct to post-operative pain management strategies, but more studies are needed in this area employing larger-scale, well-controlled clinical trial designs to evaluate the specificity of tDCS dosing strategies and to begin to elucidate possible mechanisms of action.

D. RESEARCH DESIGN AND METHODS (including data analysis)

Figure 1. Study overview and patient flow



Overview: The proposed study employs a randomized, double-blind, sham-controlled design to evaluate the effects of tDCS on pain among veterans receiving unilateral TKA or unilateral THA. Further, this study will examine dose-dependency of the tDCS analgesic effects. 120 patients undergoing TKA will be randomly assigned to one of four groups: *Group1*- 4-sessions of real tDCS, *Group2*- 2-sessions of real tDCS (+ 2 sham-sessions), *Group3*- 1-session of real tDCS (+ 3 sham-sessions), or *Group4*- 4-sessions of sham tDCS. Participants' PCA opioid pump usage will be tracked and pain and mood ratings will be collected (see figure 1). Follow-up ratings and opioid use data will be collected at 1, 3 and 6-months post-op.

Participants: Participants will be 120 patients undergoing TKA or THA surgery at the Ralph H. Johnson VAMC in Charleston SC. Inclusion/Exclusion criteria are as follows:

1) Between the ages of 25 and 90

2) No implanted medical devices above the waist

3) Mentally capable of reading, writing, giving consent, and following instructions

4) Not pregnant

5) Cleared for and scheduled for unilateral TKA or THAsurgery

6) No history of seizures

7) Not allergic to latex rubber

8) No psychiatric conditions except for depression and/or anxiety disorders as these are commonly seen in patients with chronic pain

Participants will be recruited by members of the research team from the Orthpaedic Surgery pre-operative clinic. Eligible and interested participants will be enrolled in the study during their hospital stay for TKA or THA and for the following 6-month follow-up period. Data will be psychosocial, pain and behavioral ratings, medical surgical outcomes and PCA opioid use. All data will be collected by the study investigators, clinicians and the research team.

Dependent Measures: See table-1 for the schedule of measurement.

THE BECK DEPRESSION INVENTORY (BDI) is a well-researched, brief, self-report depression screening instrument. It consists of 21-items that assess different aspects of depression (e.g., anhedonia, excessive guilt, suicidal ideation, vegetative symptoms, tearfulness). [103-108] IF ITEM #9 (SUICIDAL IDEATION) IS ENDORSED, PARTICIPANTS WILL UNDERGO A FACE-TO-FACE SELF-SAFETY SCREEN (I.E., INTERVIEW ASSESSING IDEATION, INTENT, PLAN, MEANS) AND A REFERRAL WILL BE MADE TO MENTAL HEALTH SERVICES IF NECESSARY FOR FORMAL EVALUATION AND TREATMENT AS INDICATED.

THE BECK ANXIETY INVENTORY (BAI) is a well-researched, brief self-report anxiety screening instrument. It consists of 21-items that assess different aspects of anxiety experience (e.g., physiological, cognitive, behavioral). [109]

THE BRIEF PAIN INVENTORY (BPI) is a 17-item self-report questionnaire designed to assess chronic pain intensity and the impact of pain on general functioning, relationships and mood. [110, 111]

THE MCGILL PAIN QUESTIONNAIRE (MPQ) is a 21-item self-report scale designed to capture the quality and intensity of the pain experience. [112, 113] Subjects are asked to place a mark next to appropriate descriptors of their pain. The descriptors are assigned scores and the values load onto 4 factors: 1) Sensory, 2) Affective, 3) Evaluative, and 4) Miscellaneous.

VISUAL ANALOGUE SCALE (VAS) RATING SCALES anchored with "no pain" and "worst pain imaginable" will be collected twice daily during the inpatient stay to assess pain at its worst, pain at its least, pain on average, and pain 'right now'. Additionally, participants will rate pain "Unpleasantness" using VAS in order to assess the affective component of the pain experience. The same system will be used to assess changes in mood at its worst, mood at its best, mood on average and mood 'right now' but the anchors will be "extremely depressed, sad or agitated" and "extremely good mood." This VAS method of pain assessment was chosen because it can be administered numerous times each day and it is highly sensitive to changes in pain perception and mood. VAS ratings will be collected immediately prior to, during, and immediately following all physical therapy sessions (inpatient and outpatient) during the 3-month follow-up period.

DAILY PAIN DIARY: The diary will require participants to record their average pain rating, pain at its worst, pain at its least, Activity level, Mood, sleep from previous night, and the number of times prescription pain medications were taken that day. Participants will be asked to fill out this form each day at night for the first 8 weeks post-surgery.

KNEE FLEXION MEASURE: A Gollehon Extendable Goniometer will be used to measure degrees of knee flexion at each post-operative physical rehabilitation visit.

POSTOPERATIVE COMPLICATIONS will be defined as any event, illness or postoperative occurrence that negatively impacts the health, well-being or functioning of the patients enrolled in the trial (including but not limited to headaches, confusion, delirium, nausea, vomiting, infections, and cardio-vascular complications). These events are tracked by medical staff as part of routine care, and the information will be gathered and recorded in the research database as well as length-of-stay at the time of discharge.

PATIENT CONTROLLED ANALGESIA (PCA) PUMP USAGE: After tDCS administration, patients will be started on a patient controlled analgesia (PCA) pump. For statistical analyses of PCA pump usage, morphine-equivalent analgesic dose will be calculated (e.g., 0.2 mg of hydromorphone = 1.0 mg of morphine). Initial PCA settings will consist of hydromorphone 0.2mg/dose with a lockout interval of 10 minutes. The 4-hour maximum dose will be 4.8mgs with no continuous infusion. If a patient does not tolerate hydromorphone, the PCA medication can be changed to a different opioid and morphine-equivalent dosing will be used. If pain is not adequately controlled, the patient will be reassessed by

study personnel prior to increasing the PCA dosing regimen. PCA pump usage will be downloaded from the PCA pump after discharge from the hospital.

MEDICAL OUTCOMES STUDY SHORT-FORM 36 HEALTH SURVEY (SF-36) is a 36-item measure of general health intended to capture quality of life, functional ability and well-being (mental and physical). The SF-36 will be administered pre-surgery, at discharge, 3-month and 6-month follow-up.

BEST GUESS QUESTIONNAIRE will be used to determine how accurately patients, raters and tDCS operators were able to assess which treatment the patient received. This will assess our success in masking the sham treatments. Any time a guess-confidence rating is greater than 8 (on a 0 to 10 numeric rating scale), the PI will follow-up with the participant and/or administrator in order to determine what factors contributed to this level confidence. If the guess is verified correct by the statistical support personnel and any valid systematic administrative factors are identified (e.g., the participant or tDCS administrator reports that the he/she overheard the device-masking assistant discussing the device configuration, accidentally viewed the randomization codes, or felt/heard some unique tDCS-induced sensations that led them to correctly guess the condition), the participant will remain enrolled in the study (and no feedback will be provided to the administrator or participant regarding whether the guess was correct in order to avoid providing information that may further jeopardize the blind in later subjects). The participant's data will be dropped from analyses and steps will be taken to correct the mask procedure.

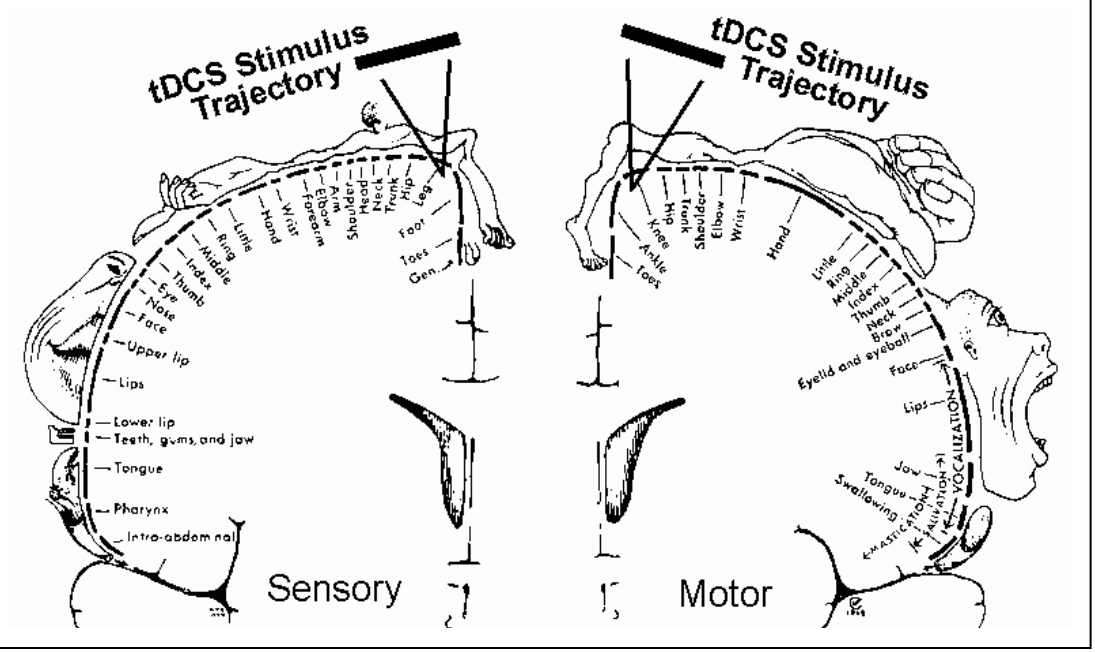
Table 1. Overview of the measurement schedule for the proposed study (POD=post-operative day)

Measure	Admission	PACU	POD-0	POD-1	POD-2	Discharge	2-weeks	4-weeks	8-weeks	3 months	6-months
BDI	X					X				X	X
BAI	X					X				X	X
BPI	X					X				X	X
SF36	X					X				X	X
PCA		X	X	X	X						
VAS		X	X	X	X		X	X	X		
MPQ		X	X	X	X		X	X	X		
Pain Diary							X	X	X		
Complications		X	X	X	X	X	X	X	X	X	X
ROM							X	X	X		
LOS						X					

Anesthesia/Surgical Measures and Procedures: Patients must be scheduled to receive unilateral total knee arthroplasty (total knee replacement) or unilateral total hip arthroplasty (total hip replacement) at the Ralph H. Johnson VAMC, to be done either cemented or cementless, either computer-assisted or conventional. The anatomical approach will be decided-upon by the surgeon based on clinical presentation, but procedure type and device manufacturer information will be recorded to permit statistical control for different procedural and device implications on post-operative pain. Preoperatively, patients will receive sedation of up to 2 mg of midazolam and 100 micrograms of fentanyl for their comfort during regional anesthesia block placement. A peripheral femoral nerve block catheter will be placed utilizing sterile technique (chloroprep, sterile glove and drape) and femoral nerve stimulation (< 0.5mA) with or without under ultrasound guidance. A 20 ml bolus of 0.5% ropivacaine will be given through the block needle prior to nerve block catheter placement. The catheter will then be placed at a depth less than 5 cm passed the needle tip and secured to the skin using sterile occlussive dressings. The patient will also receive a single injection sciatic nerve block with a 20 ml bolus of 0.5% ropivacaine utilizing nerve stimulation (< 0.5 mA) with or without ultrasound guidance. Intraoperative management

will be standardized to a general anesthetic with laryngeal mask airway or endotracheal intubation (isoflurane, fentanyl (up to 250 mcg) and succinylcholine or vecuronium). Reversal of neuromuscular blockade will be performed with neostigmine and glycopyrolate as required. Intra-articular injection of local anesthetics or opioids will not be performed in any patient. The patients will be started on the patient controlled analgesia (PCA) pump for pain. The PCA will be discontinued on post-operative day-2 at which time the patient will be transitioned to po pain medications (oxycodone). Surgery and anesthesia duration will be recorded and post-operative care will be standardized among all subjects as per standard VAMC clinical protocols.

Figure 8. Trajectory of anodal stimulation associated with the proposed tDCS electrode placement strategy



tDCS Electrode Placement: All participants will have an EEG 10-20 cap placed F3 will be marked with a non-toxic felt-tipped pen. The tDCS anode will be placed over the mark (see figure 8) and the cathode will be placed over the right dorsolateral prefrontal cortex (F4). Electrodes will be held in place with Velcro straps.

tDCS Methods: tDCS will be delivered in four 20-minute-sessions (100 minutes total) and will be conducted with the Phoresor-II Auto (Model PM850, Iomed, Salt Lake City Utah, USA) 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. Electrodes will be standard small (4cm X 4cm) sponge electrodes soaked in a sterile solution of 0.9% sodium chloride insulated by a latex casing. The current density and total charge delivered by the above parameters is consistent with those used safely in the current research literature on tDCS. A very low dose (0.125mL) of topical benzocaine (6%) cream may be applied to the skin beneath the sponge electrodes for ~10 minutes and then removed if the participant experiences strong cutaneous sensations (patient report) during stimulation. After stimulation, a vitamin-E/Aloe cream will be applied to the skin under the electrodes following each treatment to reduce risks associated with skin drying.

tDCS Dosing: Custom-developed software will be used to generate random number sequences and save them in a file-format readable by the tDCS blinding software. Participants will be randomized to one of four groups in order to assess the effects of total tDCS charge on post-operative pain.

> *Group1* will receive a total of four 20-minute sessions of active 2mA tDCS (2 sessions on post-op day 0; and 2 sessions on post-op day 1)
>
> *Group2:* will receive a total of two 20-minute sessions of active 2mA tDCS (2 sessions on post-op day 0; and 0 sessions on post-op day1) followed by 2 sessions of sham tDCS (both on post-op day 1).

Group3: will receive a only one 20-minute session of active tDCS on post-op day 0, followed by three sessions of sham tDCS (1 on post-op day 0 and 3 on post-op day 1).

Group4: will receive a total of four 20-minute sessions of sham tDCS (2 sessions on post-op day 0; and 2 sessions on post-op day 1)

This dosing scheme will permit investigators to determine whether more stimulation over time is superior to less stimulation, as well as to determine the efficacy of motor tDCS in the management of perioperative pain.

Blind Maintenance: To ensure blinding, specially-developed software will be utilized to switch the tDCS on and off 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 sessions the stimulator will be turned off following 45s. The initial sham stimulation mimics the transient scalp sensation that is perceived when the stimulator is initially switched on. The order of treatment administration will be encoded in the software so that the administrator only enters a patient number and a session-number to start stimulation without knowing whether those specific numbers area associated with active or sham tDCS. The double-blind may only be broken if the clinical presentation of the patient suggests potential cognitive dysfunction, seizure activity, severe headache or extreme skin irritation under the electrodes.

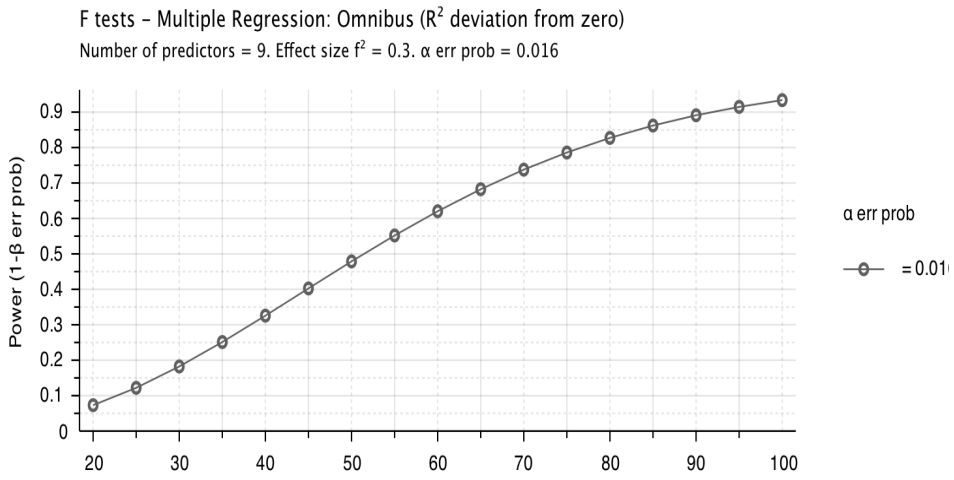
Procedures and Flow: After determining eligibility and interest, written informed consent will be obtained from participants in the Orthpaedic Surgery Pre-operative clinic. Participants will complete the screening questionnaires and all questions about the study procedures, risks, and benefits will be answered. On the day of surgery, the corresponding Admission questionnaires will be completed. After surgery, participants will be transferred to the post-anesthesia care unit (PACU), awakened, and be hooked-up to standard clinical physiological monitors. Patients will be started on a PCA pump. Pain/mood ratings will be collected and the EEG 10-20 caps will be placed. The anode and cathode placement positions will be marked and the caps will be removed. Sponge electrodes will be soaked in saline, affixed in their rubber electrode casings, attached to the tDCS machine, placed on the scalp, and held in place with Velcro straps. The participant's study ID number and tDCS session number will be entered into the tDCS controller software, linked to the randomization file, and the stimulation session will begin (double-blind). After 20-minutes, the electrodes will be removed and pain/mood ratings will be collected again. Four hours later, the tDCS procedures will be repeated in the participants' hospital room. On post-op day-1, two tDCS sessions will be conducted separated by at least 3 hours. Pain and mood ratings will be collected before and after each tDCS session. Range of motion measurements will be collected before and after each physical therapy session. On the day of discharge, participants will complete the Discharge questionnaire packet. Total length of stay, and post-surgical complications will be recorded. At all follow-up time-points, participants will complete the corresponding measures and opioid use status will be tracked via patient report and verified via chart review.

Statistical Analysis and Power: The orthopaedic surgeons at the Ralph H. Johnson VAMC conduct ~100 unilateral total knee arthroplasties and ~50 unilateral total hip arthroplasties each year . Thus, in order to meet the proposed n-size of the current study, 24 (out of 100) participants will need to be eligible and interested in participating in the trial each year. We will over recruit to permit for drop-outs and participants lost to follow-up. For analysis of primary outcomes associated with Aim-1, participants receiving any active tDCS (groups 1,2 & 3) will be collapsed and compared to the sham-only group. Multivariate multiple regression will be used with group-assignment entered into the model as a binary predictor. Surgery and anesthesia duration, depression & anxiety scores, sex, age, pre-tDCS pain, (ROM) Means and pre-op chronic opioid status will be entered into the model as covariates to permit for statistical control of these potentially confounding variables. Overall differences between real and

sham tDCS groups will then be examined for our primary outcomes: total post-op PCA morphine-equivalent dose, VAS pain-on-average ratings, and mean number of post-operative complications. Using the most conservative effect-size estimate from our series of pilot studies (d=.70), with 90 patients in the active tDCS group and 30 in the active-sham group, power is good to detect significant effects if they exist (alpha=.016 (corrected for multiple DV's); 1-ß >.80; see figure 9). For Aim-2, MANCOVA will be conducted using all 4 groups and all primary dependent measures in the same model (controlling for surgery and anesthesia duration, depression & anxiety scores, pre-tDCS pain, physical rehab measures and chronic opioid status). With four groups of 30 patients each, assuming a moderate effect size $f^2(V)=.2$, and alpha of .05, power is good detect significant main effects in the model (1-ß >.80). Secondary analyses will be conducted to evaluate long-term effects of tDCS on pain, functioning and quality of life (i.e., 2-wk, 4-wk, 8-wk, 3-month and 6 month-follow-up).

Problems/Challenges/Potential Pitfalls: The proposed tDCS device is an FDA-approved iontopohoresis device, and its use for tDCS applications is off-label. The tDCS procedure is minimal-risk and FDA-approval for tDCS applications using this device is not necessary. The PI has received MUSC IRB-approval for conducting tDCS in the perioperative setting and thus there are limited concerns about receiving approval to conduct the proposed research at the Ralph H. Johnson VAMC.

Figure 9. Power by sample-size for primary aim of the proposed study (Aim-1 target n-size = 90 patients)



Competing Trials Locally or Nationally and Distinction: The PI has an ongoing NIH-funded clinical trial of tDCS for post-operative pain at MUSC. However, that trial is focused on optimal cortical targets for stimulation (not dosing) and does not involve the veteran population. The proposed study will be on veterans and will focus on dose-dependent effects of tDCS on post-operative pain and post-surgical recovery.

Impact on Clinical Practice and Future Studies: If positive, this high-quality clinical trial could shift the paradigm of post-operative pain management to take advantage of recent neuroscience developments. Findings from this study will be used to evaluate the necessity for a multi-site clinical trial, and to develop future cross-surgical-specialty studies.

This study will be the first randomized, double-blind, controlled study of tDCS technology as an adjunctive pain management strategy for post-operative pain. Data from this trial will likely yield information regarding the feasibility and efficacy of tDCS as a post-operative pain-management approach. If the proposed pilot trial suggests significant and meaningful effects of tDCS as an adjunctive post-operative pain management strategy, this might change the way post-operative pain management is approached in the future. Findings from this study will be used to evaluate the necessity for an even larger-scale, multi-site clinical trial of the technique, and to determine whether future investigations of tDCS across different surgical specialties might be warranted.

E. PROTECTION OF HUMAN SUBJECTS

E.1. Risks to subjects

Human Subjects Involvement and Characteristics

Subjects will be 120 patients undergoing TKA and THA surgery at the Ralph H. Johnson VAMC.

Inclusion/Exclusion Criteria

1) Between the ages of 25 and 90

2) No implanted medical devices above the waist

3) Mentally capable of reading, writing, giving consent, and following instructions

4) Not pregnant

5) Cleared for and scheduled for TKA or THA surgery

6) No history of seizures

7) Not allergic to latex rubber

Sources of Material

Participants will be enrolled in the study during their hospital stay for TKA or THA and for the following 6 month follow-up period. Data will be psychosocial, pain and behavioral ratings, medical surgical outcomes and PCA opioid use. All data will be collected by the study investigators, clinicians and the research team.

Potential Risks

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. The effect-size of tDCS for post-operative pain appears to be moderate and therefore does not eliminate pain entirely. Nonetheless, if a participant experiences total analgesia via tDCS (which is believed to be an extremely unlikely occurrence as it has never been reported in any of the 1000+ participants who have received tDCS for pain control around the world), it is possible that they might not receive signals indicating over-extension or over-use of their knee(s) after surgery and might incur damage in the joint(s).

Safety in case of pregnancy*:*

Pregnant women will be excluded from the proposed research.

Risks regarding Confidentiality

Despite efforts to maintain subjects' anonymity and confidentiality, there is always some minimal risk of people other than the study investigators gaining access to subjects' information. Every effort will be made to ensure that subject information will be collected and stored in a manner that ensures the highest level of protection of confidentiality.

E.2. Adequacy of Procedures for Protecting and Minimizing Risk:

Recruitment and Informed Consent

Patients scheduled to undergo TKA or THA surgery at the Ralph H. Johnson VAMC will be recruited during their pre-operative visit in the Orthopedic Surgery Clinic. A letter of invitation will be mailed to perspective participants whom medical staff on the study feel may be eligible to participate in the approved research. These prospective subjects that will receive letters will be identified through clinic referrals from the Ralph H. Johnson VA in Charleston, Sc. A HIPAA waiver of authorization will be on file with the IRB giving the research team permission send IRB approved generic letters of invitation to perspective participants. Written-informed consent will be obtained during this pre-op visit.

Protection against Risks

There are 3 areas in which safeguards to protect subjects from undue risk require discussion. These include the procedures used to obtain informed consent, the procedures used to ensure confidentiality of the subjects' data, and the procedures used to minimize possible risks associated with the laboratory procedures.

Informed Consent. In the consent forms and discussions with an investigator, subjects are advised fully of the procedures to be used, the amount of time required of them, the research procedures that will be conducted, the possible risks and benefits of the procedures, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the Principal Investigator. All subjects will be required to have capacity to consent.

*Confidentiality of Subjects' Responses***.** In the informed consent form, subjects are told that the information they provide and all findings will be kept strictly confidential, with access limited to the research staff and the possible exception of state or federal regulatory personnel. No one but the project staff has access to the master list linking subjects' names to code numbers, and all information obtained is coded. The respective master lists are kept under strict lock and key.

*Research Procedures***.** We have described above the potential risks of the research procedures. If the subject shows deterioration in their clinical status, we will stop him/her from proceeding in the study, and coordinate appropriate care with a physician at the Ralph H. Johnson VAMC.

Participation in the study will be treated as confidential, as will all records. We will protect the identity of our subjects by keeping the data in file cabinets in the PI's locked office, to which only they have a key and by storing electronic data on secure servers designed for use and access by Brain Stimulation Lab members only.

*Data and Safety Monitoring Board***.** Dr. Borckardt will choose a group of faculty at the VAMC to monitor the data on a bi-annual basis with respect to subject safety issues throughout the award period.

E.3. Potential benefits of the proposed research to the subjects and others

Participants will receive little clinical benefit from participating in the study although 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.

E.4. Importance of the knowledge to be gained

The proper control of acute and chronic pain is one of the most important areas of health care. Despite the profound advances in neuroscience over the past 20 years, we still largely use opiate narcotics for pain control. Total joint replacement procedures involving the knees and hips are some of the most common orthopedic procedures performed. Because the prevalence of arthritis is expected to grow substantially as the population ages, these procedures are likely to become even more common. Adequate postoperative pain control is an important factor in determining recovery time and hospital length of stay. Primary methods used to manage post-operative pain in general involve systemic opioid or other analgesic drug delivery and regional blocks. Despite these pain-management strategies, patients still report considerable post-operative pain, and often struggle to complete post-operative physical therapy regimens. Further, systemic opioid analgesic use, has associated side-effects that can lead to post-operative complications including but not limited to mental-clouding, confusion, respiratory depression, interactions with other medications, addiction in some cases, fatigue, and gastric motility problems. New analgesic strategies are needed that can be used adjunctively to existing strategies with the potential to reduce reliance on opioid analgesia. In two independent pilot studies, the investigators have shown that tDCS can reduce post-operative PCA use by as much as 46% while simultaneously reducing subjective pain ratings. Thus, there appears to be potential analgesic effects of tDCS for post-procedural and post-operative pain. If it proves to be beneficial, this technique could revolutionize current methods for post-operative pain management.

Total Planned Enrollment: 120

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	4	2	6
Not Hispanic or Latino	66	48	114
Ethnic Category: Total of All Subjects*	120		
Racial Categories			
American Indian/Alaska Native	1	1	2
Asian	4	2	6
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	24	16	40
White	40	30	70
Racial Categories: Total of All Subjects*			120

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

F. REFERENCES/LITERATURE CITATIONS

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

Literature Cited

1. Orthopedic_Network_News, Hip and Knee Implant Review. CMS MedPar, 2002. pmc-id:

2. Acheson, R.M. and A.B. Collart, New Haven survey of joint diseases. XVII. Relationship between some systemic characteristics and osteoarthrosis in a general population. Ann Rheum Dis, 1975. 34(5): p. 379-387. pmc-id: 1006437

3. Peyron, J., Osteoarthritis. The epidemiologic viewpoint. Clin Orthrop, 1986. 213: p. 13-19. pmc-id:

4. Capdevila, X., Y. Barthelet, P. Biboulet, et al., Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. Anesthesiology, 1999. 91(1): p. 8-15. pmc-id:

5. Chelly, J.E., J. Greger, R. Gebhard, et al., Continuous femoral blocks improve recovery and outcome of patients undergoing total knee arthroplasty. J Arthroplasty, 2001. 16(4): p. 436-445. pmc-id:

6. Wang, H., B. Boctor, and J. Verner, The effect of single-injection femoral nerve block on rehabilitation and length of hospital stay after total knee replacement. Reg Anesth Pain Med, 2002. 27(2): p. 139-144. pmc-id:

7. Deo, H., G. West, C. Butcher, et al., The prevalence of cognitive dysfunction after conventional and computer-assisted total knee replacement. Knee. pmc-id:

8. Talmo, C.T., C.E. Robbins, and J.V. Bono, Total joint replacement in the elderly patient. Clin Geriatr Med. 26(3): p. 517-529. pmc-id:

9. Samson, A.J., G.E. Mercer, and D.G. Campbell, Total knee replacement in the morbidly obese: a literature review. ANZ J Surg. 80(9): p. 595-599. pmc-id:

10. Fregni, F., S. Freedman, and A. Pascual-Leone, Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. Lancet Neurol, 2007. 6(2): p. 188-191. pmc-id:

11. Rosen, A.C., M. Ramkumar, T. Nguyen, et al., Noninvasive transcranial brain stimulation and pain. Curr Pain Headache Rep, 2009. 13(1): p. 12-17. pmc-id: 2697608

12. Williams, J.A., M. Imamura, and F. Fregni, Updates on the use of non-invasive brain stimulation in physical and rehabilitation medicine. J Rehabil Med, 2009. 41(5): p. 305-311. pmc-id:

13. George, M.S., Z. Nahas, F.A. Kozol, et al., Mechanisms and the current state of transcranial magnetic stimulation. CNS Spectr, 2003. 8(7): p. 496-514. pmc-id:

14. Barker, A., I. Freeston, J. Jarratt, et al., Magnetic stimulation of the human nervous system: an introduction and basic principles, in Magnetic Stimulation in Clinical Neurophysiology, C. S, Editor. 1989, Butterworth: Boston. p. 55-72.

15. Barker, A.T., R. Jalinous, and I.L. Freeston, Non-invasive magnetic stimulation of human motor cortex. Lancet, 1985. 1(8437): p. 1106-1107. pmc-id:

16. Knotkova, H. and R.A. Cruciani, Non-invasive transcranial direct current stimulation for the study and treatment of neuropathic pain. Methods Mol Biol. 617: p. 505-515. pmc-id:

17. Mori, F., C. Codeca, H. Kusayanagi, et al., Effects of Anodal Transcranial Direct Current Stimulation on Chronic Neuropathic Pain in Patients With Multiple Sclerosis. J Pain, 2009. pmc-id:

18. Boggio, P.S., E.J. Amancio, C.F. Correa, et al., Transcranial DC stimulation coupled with TENS for the treatment of chronic pain: a preliminary study. Clin J Pain, 2009. 25(8): p. 691-695. pmc-id:

19. 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:

20. Boggio, P.S., S. Zaghi, M. Lopes, et al., 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:

21. Antal, A., N. Brepohl, C. Poreisz, et al., Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. Clin J Pain, 2008. 24(1): p. 56-63. pmc-id:

22. Roizenblatt, S., F. Fregni, R. Gimenez, et al., Site-specific effects of transcranial direct current stimulation on sleep and pain in fibromyalgia: a randomized, sham-controlled study. Pain Pract, 2007. 7(4): p. 297-306. pmc-id:

23. Fregni, F., D. DaSilva, K. Potvin, et al., Treatment of chronic visceral pain with brain stimulation. Ann Neurol, 2005. 58(6): p. 971-972. pmc-id:

24. Fregni, F., R. Gimenes, A.C. Valle, et al., A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. Arthritis Rheum, 2006. 54(12): p. 3988-3998. pmc-id:

25. Avery, D.H., P.E. Holtzheimer, 3rd, W. Fawaz, et al., Transcranial magnetic stimulation reduces pain in patients with major depression: a sham-controlled study. J Nerv Ment Dis, 2007. 195(5): p. 378-381. pmc-id:

26. 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:

27. Borckardt, J.J., S.T. Reeves, M. Weinstein, 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

28. Borckardt, J.J., A.R. Smith, S.T. Reeves, 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:

29. Borckardt, J.J., A.R. Smith, S.T. Reeves, 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

30. Borckardt, J.J., M. Weinstein, S.T. Reeves, et al., Post-Operative Left Prefrontal Repetitive Transcranial Magnetic Stimulation (rTMS) Reduces Patient-Controlled Analgesia Use Anesthesiology, 2006. 105: p. 557-562. pmc-id:

31. Morgan, D., K. Forst-Pineda, and M. Gold, Medical and nonmedical use of prescription opioids: Epidemiology and Prevalence. Psychiatric Annals, 2006. 36(6): p. 404-409. pmc-id:

32. Alam, A., T. Gomes, H. Zheng, et al., Long-term analgesic use after low-risk surgery: a retrospective cohort study. Arch Intern Med. 172(5): p. 425-430. pmc-id:

33. Greer, S.M., J.A. Dalton, J. Carlson, et al., Surgical patients' fear of addiction to pain medication: the effect of an educational program for clinicians. Clin J Pain, 2001. 17(2): p. 157-164. pmc-id:

34. Compton, W.M. and N.D. Volkow, Major increases in opioid analgesic abuse in the United States: concerns and strategies. Drug Alcohol Depend, 2006. 81(2): p. 103-107. pmc-id:

35. Kehlet, H., M. Werner, and F. Perkins, Balanced analgesia: what is it and what are its advantages in postoperative pain? Drugs, 1999. 58(5): p. 793-797. pmc-id:

36. Dowman, R., G. Glebus, and L. Shinners, Effects of response conflict on pain-evoked medial prefrontal cortex activity. Psychophysiology, 2005. 42(5): p. 555-558. pmc-id:

37. Ginandes, C., P. Brooks, W. Sando, et al., Can medical hypnosis accelerate post-surgical wound healing? Results of a clinical trial. Am J Clin Hypn, 2003. 45(4): p. 333-351. pmc-id:

38. Montgomery, G.H., C.R. Weltz, M. Seltz, et al., Brief presurgery hypnosis reduces distress and pain in excisional breast biopsy patients. Int J Clin Exp Hypn, 2002. 50(1): p. 17-32. pmc-id:

39. Good, M., G.C. Anderson, S. Ahn, et al., Relaxation and music reduce pain following intestinal surgery. Res Nurs Health, 2005. 28(3): p. 240-251. pmc-id:

40. Voss, J.A., M. Good, B. Yates, et al., Sedative music reduces anxiety and pain during chair rest after open-heart surgery. Pain, 2004. 112(1-2): p. 197-203. pmc-id:

41. Cheung, Y.L., A. Molassiotis, and A.M. Chang, A pilot study on the effect of progressive muscle relaxation training of patients after stoma surgery. Eur J Cancer Care (Engl), 2001. 10(2): p. 107-114. pmc-id:

42. Cheung, Y.L., A. Molassiotis, and A.M. Chang, The effect of progressive muscle relaxation training on anxiety and quality of life after stoma surgery in colorectal cancer patients. Psychooncology, 2003. 12(3): p. 254-266. pmc-id:

43. Feldman, J.B., The neurobiology of pain, affect and hypnosis. Am J Clin Hypn, 2004. 46(3): p. 187-200. pmc-id:

44. Feldman, M., M. MacCulloch, J. Orford, et al., The application of anticipatory avoidance learning to the treatment of homosexuality. Developments in treatment technique and response recording. Acta Psychiatr Scand, 1969. 45(2): p. 109-117. pmc-id:

45. Gatchel, R.J., Y.B. Peng, M.L. Peters, et al., The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull, 2007. 133(4): p. 581-624. pmc-id:

46. Treede, R.D., D.R. Kenshalo, R.H. Gracely, et al., The cortical representation of pain. Pain, 1999. 79(2-3): p. 105-111. pmc-id:

47. Greer, K.R. and J.W. Hoyt, Pain: theory, anatomy, and physiology. Crit Care Clin, 1990. 6(2): p. 227-234. pmc-id:

48. Crue, B.L., B. Kenton, and E.J. Carregal, Neurophysiology of pain-peripheral aspects. Speculation concerning the possibility of a unitary peripheral cutaneous input system for pressure, hot, cold and tissue damage. Bull Los Angeles Neurol Soc, 1976. 41(1): p. 13-42. pmc-id:

49. Dyck, P.J., E.H. Lambert, and P.C. O'Brien, Pain in peripheral neuropathy related to rate and kind of fiber degeneration. Neurology, 1976. 26(5): p. 466-471. pmc-id:

50. Staud, R., M.E. Robinson, C.J. Vierck, Jr., et al., Ratings of experimental pain and pain-related negative affect predict clinical pain in patients with fibromyalgia syndrome. Pain, 2003. 105(1-2): p. 215-222. pmc-id:

51. Burns, J.W., A. Kubilus, and E. Michael, Cognitive-Behavioral Factors in the Management of Chronic Low Back Pain: Conceptualization and Evidence of Treatment Efficacy. Curr Rev Pain, 1999. 3(4): p. 300-307. pmc-id:

52. Giardino, N.D., M.P. Jensen, J.A. Turner, et al., Social environment moderates the association between catastrophizing and pain among persons with a spinal cord injury. Pain, 2003. 106(1-2): p. 19-25. pmc-id:

53. Atkinson, J.H., M.A. Slater, D.R. Wahlgren, et al., Effects of noradrenergic and serotonergic antidepressants on chronic low back pain intensity. Pain, 1999. 83(2): p. 137-145. pmc-id:

54. Brooks, J.C., T.J. Nurmikko, W.E. Bimson, et al., fMRI of thermal pain: effects of stimulus laterality and attention. Neuroimage, 2002. 15(2): p. 293-301. pmc-id:

55. Davis, K.D., Neurophysiological and anatomical considerations in functional imaging of pain. Pain, 2003. 105(1-2): p. 1-3. pmc-id:

56. 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:

57. 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:

58. Theunissen, M., M.L. Peters, J. Bruce, et al., Preoperative Anxiety and Catastrophizing: A Systematic Review and Meta-analysis of the Association With Chronic Postsurgical Pain. Clin J Pain. pmc-id:

59. Zubieta, J.K., J.A. Bueller, L.R. Jackson, et al., Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. J Neurosci, 2005. 25(34): p. 7754-7762. pmc-id:

60. Wager, T.D., J.K. Rilling, E.E. Smith, et al., Placebo-induced changes in FMRI in the anticipation and experience of pain. Science, 2004. 303(5661): p. 1162-1167. pmc-id:

61. Tsubokawa, T., Y. Katayama, T. Yamamoto, et al., Treatment of thalamic pain by chronic motor cortex stimulation. Pacing Clin Electrophysiol, 1991. 14(1): p. 131-134. pmc-id:

62. Tsubokawa, T., Y. Katayama, T. Yamamoto, et al., Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir Suppl (Wien), 1991. 52: p. 137-139. pmc-id:

63. Lefaucheur, J.P., G. Jarry, X. Drouot, et al., Motor cortex rTMS reduces acute pain provoked by laser stimulation in patients with chronic neuropathic pain. Clin Neurophysiol. 121(6): p. 895-901. pmc-id:

64. Peyron, R., I. Faillenot, P. Mertens, et al., Motor cortex stimulation in neuropathic pain. Correlations between analgesic effect and hemodynamic changes in the brain. A PET study. Neuroimage, 2007. 34(1): p. 310-321. pmc-id:

65. Garcia-Larrea, L. and R. Peyron, Motor cortex stimulation for neuropathic pain: From phenomenology to mechanisms. Neuroimage, 2007. 37 Suppl 1: p. S71-79. pmc-id:

66. George, M.S., Z. Nahas, F.A. Kozel, et al., Mechanisms and state of the art of transcranial magnetic stimulation. J Ect, 2002. 18(4): p. 170-181. pmc-id:

67. Roth, B.J., S. Momen, and R. Turner, Algorithm for the design of magnetic stimulation coils. Med & Biol Eng & Comput, 1994. 32: p. 214-216. pmc-id:

68. Stanton, P.K. and T.J. Sejnowski, Associative long-term depression in the hippocampus induced by hebbian covariance. Nature, 1989. 339(6221): p. 215-218. pmc-id:

69. Malenka, R.C. and R.A. Nicoll, Long-term potentiation--a decade of progress? Science, 1999. 285(5435): p. 1870-1874. pmc-id:

70. Wang, H., X. Wang, and H. Scheich, LTD and LTP induced by transcranial magnetic stimulation in auditory cortex. Neuroreport, 1996. 7(2): p. 521-525. pmc-id:

71. Wassermann, E.M. and J. Grafman, Recharging cognition with DC brain polarization. Trends Cogn Sci, 2005. 9(11): p. 503-505. pmc-id:

72. Lefaucheur, J.P., X. Drouot, Y. Keravel, et al., Pain relief induced by repetitive transcranial magnetic stimulation of precentral cortex. Neuroreport, 2001. 12(13): p. 2963-2965. pmc-id:

73. George, M.S. and E.M. Wassermann, Rapid-rate transcranial magnetic stimulation and ECT. Convuls Ther, 1994. 10(4): p. 251-254; discussion 255-258. pmc-id:

74. 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:

75. Wagner, T., A. Valero-Cabre, and A. Pascual-Leone, Noninvasive human brain stimulation. Annu Rev Biomed Eng, 2007. 9: p. 527-565. pmc-id:

76. Miranda, P.C., M. Lomarev, and M. Hallett, Modeling the current distribution during transcranial direct current stimulation. Clin Neurophysiol, 2006. 117(7): p. 1623-1629. pmc-id:

77. 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:

78. Nitsche, M.A., L.G. Cohen, E.M. Wassermann, et al., Transcranial direct current stimulation: State of the art 2008. Brain Stimul, 2008. 1(3): p. 206-223. pmc-id:

79. Antal, A., T.Z. Kincses, M.A. Nitsche, et al., Manipulation of phosphene thresholds by transcranial direct current stimulation in man. Exp Brain Res, 2003. 150(3): p. 375-378. pmc-id:

80. Lang, N., H.R. Siebner, Z. Chadaide, et al., Bidirectional modulation of primary visual cortex excitability: a combined tDCS and rTMS study. Invest Ophthalmol Vis Sci, 2007. 48(12): p. 5782-5787. pmc-id:

81. Migita, K., T. Uozumi, K. Arita, et al., Transcranial magnetic coil stimulation of motor cortex in patients with central pain. Neurosurgery, 1995. 36(5): p. 1037-1039; discussion 1039-1040. pmc-id:

82. Tamura, Y., S. Okabe, T. Ohnishi, et al., Effects of 1-Hz repetitive transcranial magnetic stimulation on acute pain induced by capsaicin. Pain, 2004. 107(1-2): p. 107-115. pmc-id:

83. Rollnik, J.D., S. Wustefeld, J. Dauper, et al., Repetitive transcranial magnetic stimulation for the treatment of chronic pain - a pilot study. Eur Neurol, 2002. 48(1): p. 6-10. pmc-id:

84. Pleger, B., F. Janssen, P. Schwenkreis, et al., Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. Neurosci Lett, 2004. 356(2): p. 87-90. pmc-id:

85. Lefaucheur, J.P., X. Drouot, and J.P. Nguyen, Interventional neurophysiology for pain control: duration of pain relief following repetitive transcranial magnetic stimulation of the motor cortex. Neurophysiol Clin, 2001. 31(4): p. 247-252. pmc-id:

86. Lefaucheur, J.P., X. Drouot, I. Menard-Lefaucheur, et al., Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. J Neurol Neurosurg Psychiatry, 2004. 75(4): p. 612-616. pmc-id: 1739005

87. Canavero, S. and V. Bonicalzi, Central pain syndrome: elucidation of genesis and treatment. Expert Rev Neurother, 2007. 7(11): p. 1485-1497. pmc-id:

88. Khedr, E.M., H. Kotb, N.F. Kamel, et al., Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J Neurol Neurosurg Psychiatry, 2005. 76(6): p. 833-838. pmc-id: 1739662

89. Borckardt, J.J., S.T. Reeves, W. Beam, et al., A Randomized, Controlled Investigation of Motor Cortex Transcranial Magnetic Stimulation (TMS) Effects on Quantitative Sensory Measures in Healthy Adults: Evaluation of TMS Device Parameters. Clin J Pain. pmc-id:

90. Nitsche, M.A., A. Seeber, K. Frommann, et al., Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. J Physiol, 2005. 568(Pt 1): p. 291-303. pmc-id: PMC1474757

91. Antal, A., D. Terney, S. Kuhnl, et al., 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:

92. Lavoie, B.A., H. Devanne, and C. Capaday, Differential control of reciprocal inhibition during walking versus postural and voluntary motor tasks in humans. J Neurophysiol, 1997. 78(1): p. 429-438. pmc-id:

93. Devanne, H., B.A. Lavoie, and C. Capaday, Input-output properties and gain changes in the human corticospinal pathway. Exp Brain Res, 1997. 114(2): p. 329-338. pmc-id:

94. Ridding, M.C. and J.C. Rothwell, Stimulus/response curves as a method of measuring motor cortical excitability in man. Electroencephalogr Clin Neurophysiol, 1997. 105(5): p. 340-344. pmc-id:

95. Bachmann, C.G., S. Muschinsky, M.A. Nitsche, et al., Transcranial direct current stimulation of the motor cortex induces distinct changes in thermal and mechanical sensory percepts. Clin Neurophysiol. pmc-id:

96. Jurgens, T.P., A. Schulte, T. Klein, et al., 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:

97. Borckardt, J.J., M. Bikson, H. Frohman, 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:

98. Johnson, S., J. Summers, and S. Pridmore, Changes to somatosensory detection and pain thresholds following high frequency repetitive TMS of the motor cortex in individuals suffering from chronic pain. Pain, 2006. 123(1-2): p. 187-192. pmc-id:

99. Leo, R.J. and T. Latif, Repetitive transcranial magnetic stimulation (rTMS) in experimentally induced and chronic neuropathic pain: a review. J Pain, 2007. 8(6): p. 453-459. pmc-id:

100. Craig, A.D., K. Chen, D. Bandy, et al., Thermosensory activation of insular cortex. Nat Neurosci, 2000. 3(2): p. 184-190. pmc-id:

101. Davis, K.D., C.L. Kwan, A.P. Crawley, et al., Functional MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli. J Neurophysiol, 1998. 80(3): p. 1533-1546. pmc-id:

102. Borckardt, J.J., J. Romagnuolo, S.T. Reeves, 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:

103. Taylor, R., P.F. Lovibond, M.K. Nicholas, et al., The utility of somatic items in the assessment of depression in patients with chronic pain: a comparison of the Zung Self-Rating Depression Scale and the

Depression Anxiety Stress Scales in chronic pain and clinical and community samples. Clin J Pain, 2005. 21(1): p. 91-100. pmc-id:

104. Faravelli, C., G. Albanesi, and E. Poli, Assessment of depression: a comparison of rating scales. J Affect Disord, 1986. 11(3): p. 245-253. pmc-id:

105. Tanaka-Matsumi, J. and V.A. Kameoka, Reliabilities and concurrent validities of popular self-report measures of depression, anxiety, and social desirability. J Consult Clin Psychol, 1986. 54(3): p. 328-333. pmc-id:

106. Gould, J., A psychometric investigation of the standard and short form Beck Depression Inventory. Psychol Rep, 1982. 51(3 Pt 2): p. 1167-1170. pmc-id:

107. Reynolds, W.M. and J.W. Gould, A psychometric investigation of the standard and short form Beck Depression Inventory. J Consult Clin Psychol, 1981. 49(2): p. 306-307. pmc-id:

108. Beck, A.T. and A. Beamesderfer, Assessment of depression: the depression inventory. Mod Probl Pharmocopsychiatry, 1974. 7(0): p. 151-169. pmc-id:

109. Beck, A.T., N. Epstein, G. Brown, et al., An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol, 1988. 56(6): p. 893-897. pmc-id:

110. Daut, R.L., C.S. Cleeland, and R.C. Flanery, Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain, 1983. 17(2): p. 197-210. pmc-id:

111. Tan, G., M.P. Jensen, J.I. Thornby, et al., Validation of the Brief Pain Inventory for chronic nonmalignant pain. J Pain, 2004. 5(2): p. 133-137. pmc-id:

112. Gagliese, L. and J. Katz, Age differences in postoperative pain are scale dependent: a comparison of measures of pain intensity and quality in younger and older surgical patients. Pain, 2003. 103(1-2): p. 11-20. pmc-id:

113. Zalon, M.L., Comparison of pain measures in surgical patients. J Nurs Meas, 1999. 7(2): p. 135-152. pmc-id:

H. FACILITES AVAILABLE

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

The PI (an independent investigator in the Brain Stimulation Laboratory) possesses the tDCS machine described in this protocol. Participants will be involved in a standard clinical protocol and will have all of the resources available to them and to manage their post-operative disposition that all patients would have at VAMC.