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Brief Title: Adjunctive Transcranial Direct Current Stimulation (tDCS)

Official Title: A Single-Blind, Randomized Control Trial of Adjunctive Transcranial Direct Current Stimulation (tDCS) for Chronic Pain Among Patients Receiving Specialized, Inpatient Multi-Modal Pain Management

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Participants

We enrolled adult participants who are ≥18 years old and were admitted to the Pain Management Program at The Menninger Clinic in Houston, Texas. Patients presented with multiple and myriad chronic pain concerns, such as: testicular pain, vaginal floor pain, chronic regional pain syndrome (CRPS) of the foot, headache (migraine, cluster), lower back pain (e.g., L4-L5 herniation), and upper back pain (post cervical fusion). Additionally, each patient presented with significant co-morbid psychiatric burden of illness, such as multiple axis I disorders (e.g. major depressive disorder, anxiety-spectrum disorders, and the like) with maladaptive personality traits (including formal diagnoses of personality disorders), severe and chronic suicidal ideation (and attempts) as well as multiple previous outpatient providers and hospitalizations. The Pain Management Program itself did not specialize in the treatment of a particular chronic pain etiology, and as such, there was significant heterogeneity in terms of pain syndromes as well as co-morbid psychiatric concerns. For this study, CP was defined as pain lasting over 6 months or with duration longer than expected for its natural course of recovery and with a self-reported average intensity of 4 / 10 or greater within the past 24 hours. Women were eligible following a confirmed negative pregnancy test (which is conducted within 24 hours of admission to the hospital as part of standard clinical care). Exclusion criteria were active psychosis and cognitive impairment. Patients with preexisting irritation, cuts, or lesions where the tDCS electrodes were to be placed (i.e., the forehead) were excluded from the study. Participants had to have been free of unstable medical conditions, or conditions that may increase the risk of seizure, such as uncontrolled epilepsy. Patients with a history of severe cranial trauma with alteration of the cranial anatomy or metallic intracranial implants were excluded. Potential participants with known sensitivity to Lidocaine 4% were not eligible. Patients with documented Raynaud's phenomenon were not eligible given potential safety concerns (Birnie et al., 2012) associated with this condition and one of the outcome measures (Cold Pressor Test, discussed below). Recruitment of potential participants was limited to patients admitted to the Pain Management Program at The Menninger Clinic; they were contacted through direct verbal communication by a member of the research team.

An a priori power analysis was estimated based on modest effect sizes for the analgesic benefit of tDCS ($d = .51$; $f = .25$) in the existing literature (DaSilva et al 2012), indicating that a total of 70 participants (35 per group assigned through replacement randomization to the active tDCS or the sham tDCS conditions) was needed to detect an effect (alpha = .05, effect size $f = .25$, correlation among repeated measures = .5) with adequate power ($1 - \beta = 0.80$). To include the potential for early termination, we estimate a

conservative 20% drop out rate for the final sample size calculation. As such, we planned to enroll 84 participants in the study.

Materials

Device & Associated Peripherals

The tDCS device is a battery-powered direct and constant current stimulator (Soterix Medical Inc. 2014). The selected tDCS device used in this study is certified for good manufacturing practice indicative of its non-significant risk, a requirement expected for Investigational Device Exceptions (IDE) as defined by the Food and Drug Administration (FDA), Department of Health and Human Services (United States Food and Drug Administration 2015). Real tDCS was applied by supplying 2 mA (current density=.057 A/m2) during each stimulation session.

Neurotargeting tDCS-explorer® software, Version 2.3 (Soterix Medical Inc. 2013) was used to localize the placement of the electrodes. Each rubber electrode was inserted into 5 X 7 cm (35cm2) sponge-pads, which were soaked with 12 ml of saline solution (Baxter Healthcare Corp. 0.9% Sodium Chloride Irrigation, USP). Electrodes were held in place on participants' foreheads using sized plastic fasteners (Soterix Medical Inc. 2014).

Pre- and post-stimulation skin treatment

Prior to simulation participants cleaned the skin over their foreheads with single use alcohol preps (70% isopropyl; Covidien 2011) and allowed it to dry. This reduced the likelihood that other chemicals (e.g. lotions, makeup, etc.) would interfere with stimulation. To reduce the likelihood of irritation related to electrical stimulation, a low dose (1/8 of an inch) topical lidocaine (4%) cream was then applied to the skin. Skin pretreatment with a topical anesthetic has demonstrated benefit in reducing mild irritation associated with both active and sham tDCS conditions (Guarienti et al 2014). Although side-effects from lidocaine (4%) cream are rare (Baumann et al 2010, Oni et al 2010), patient safety was assured by waiting for a 3-minute period where participants are asked to report any potential discomfort associated with the use of lidocaine. The trial was discontinued if a participant responded affirmatively. To minimize the likelihood of skin irritation after each tDCS session (Naylor et al 2014), vitamin-E oil (400 Unit; Rugby) wa applied to the skin where the electrodes were placed.

Design

The research design was developed in line with requirements for a Phase II, Single Center Device Study as defined by the FDA (United States Food and Drug Administration 2015). In this superiority trial. participants who meet inclusion criteria are randomized (1:1) into a single-blind, 2x12 (group X time) controlled trial. Participants were assigned to one of two groups: active tDCS plus usual care or sham tDCS plus usual care. Only the administrating research staff member and PI were aware of tDCS condition applied. Participant's clinical outcomes are collected daily during each day of stimulation as well as weekly for two weeks following the active phase of the trial Data will be collected for 22 days during the following days: days 1-5, days 8-12, day 15, and day 22.

Procedures

Pre-consent procedures

Participants were engaged between one day and four weeks in research related activities depending on inclusion/exclusion criteria. During the first week that patients were receiving treatment in the Pain Management Program at The Menninger Clinic, potential participants were provided a brief overview of the study and disclosure of waiver for written documentation of informed consent when choosing to participate in the pre-screening interview. The prescreening interview consisted of self-report of yes or no responses to the previously described inclusion and exclusion criteria. For potential participants who met inclusion criteria and were willing to participate in the study, a member of the research team reviewed each facet of the informed consent and answered any questions that he/she might have. Prospective female participants were informed of the need for review of medical health records to confirm a negative pregnancy test result. No compensation or stipend was provided for participating in the study. Participants were required to sign a Baylor College of Medicine Institutional Review Board (protocol number H36721)-approved consent form. Consented participants were provided a calendar with appointments scheduled for each day they are projected to participate in the study.

Brain Stimulation Procedures

Participants received anodal stimulation over the left DLPFC and cathodal stimulation over the right DLPFC – F3, F4, respectively, according to the International 10-20 EEG System for Positioning (Herwig et al 2003) and localized based on Neurotargeting tDCS-explorer® software, Version 2.3 (Soterix Medical Inc. 2013). This placement was consistent with the published prefrontal tDCS studies for pain to date (Bartholomew et al 1997, Brunoni et al 2012, Rego et al 2015). Participants received brain stimulation for 20 minutes per session over the course of 2 work weeks: 5 consecutive days (Monday – Friday) of stimulation followed by a 2 day break (Saturday and Sunday) and then again for 5 days of stimulation, for a total of 200 minutes of brain stimulation. Participants randomized to active tDCS receive a constant current of 2 mA that automatically ramped down to 0mA at the end of each session.

Participants randomized to the sham condition underwent the same procedures as those in the active tDCS sample, including: the same localization of electrode placement, actual placement of electrodes, turning on the tDCS equipment, as well as a brief (30 seconds) tingling sensation over their forehead evoked by active tDCS stimulation at the start of the sham stimulation. Other than this brief stimulation, participants randomized to sham tDCS do not receive active stimulation (0 mA) during the 20 minutes of the session. Other methods applied to reduce the likelihood of blinding being compromised include: 1) delaying retrieval of the device until the patient was seated and had the electrodes placed on his/her forehead; and 2) shielding the tDCS device with a paper cover and placing it behind the peripheral view of participants. To further assure blinding, members of the inpatient treatment team were not informed of participants' randomization status. Participants were not informed of received active or sham tDCS. Throughout the study participants are provided reminders about the voluntary nature of participation.

Location of the research center within an inpatient setting supported access and adherence to scheduled visits, especially those recurring on a daily basis. The Pain Management Program's administrative staff provided ongoing support through reminders for each research visit and coordinated appointments for research related activities. Further, to avoid disruption of scheduled therapeutic activities that patients engaged in as part of the Pain Management Program, tDCS sessions were completed during late afternoon hours.

Assessment Procedures

Participants completed self-report and performance-based assessments daily during each day of stimulation (prior to the actual stimulation) as well as weekly for two weeks following the active phase of the trial. Data were collected for 22 days during the following days: days 1-5, days 8-12, day 15, and day 22. Self-report assessments are collected via Chronic Pain Tracker version 3.6, an iPad interfaced application (See Figures 3 and 4; (Chronic Stimulation 2015). Participants were asked to rate their experience during the past 24 hours across the following domains: pain intensity (on a 0-10 visual analogue scale; outcome measure for primary aim), pain triggers (from a list of 10 common pain triggers; outcome measure for primary aim), pain description (using descriptors from the McGill Pain Questionnaire, (Melzack 1987), sleep history (including total duration, time to sleep onset, use of sleep aids, subjective rating of sleep quality [0-10 point Likert-scale]; outcome measure for secondary aim), and physical activity level (on a 0-10 point Likert-scale from light to heavy; outcome measure for secondary aim).

The performance-based pain tolerance task was completed through the cold presser task (CPT; (Edens & Gil 1995). This task allowed for a measurement of induced pain by placing participants' non-dominant hand in cold water, a stimulus that yields slow and progressively escalating pain from mild to moderate intensity with the participant in complete control of when to withdrawal the limb from the cold water (von Baeyer et al 2005). Because CPT can simulate the CP experience, it is considered an essential component to reliably measure pain in intervention trials (Mitchell et al 2004). Specifically, participants were asked to submerse (up to the forearm) their non-dominant hand with the palm facing up, in a tub of cold water (5°C), and to "keep the hand submersed until the water is too uncomfortable to continue" (Mitchell et al 2004, Rainville et al 1992). Participants were then asked to keep their hand still, as studies have shown movement may alleviate the discomfort evoked by temperature changes. Upon removing the hand from the CPT, participants were provided with a towel to warm and/or soothe any discomfort resulting from the submersion (e.g. mild pain and numbness; (Helsen et al 2011). The maximum submersion time was limited by the experimenters to 5 minutes. The temperature (5°C) and maximum duration (5 minutes) of submersion has been used in multiple trials and is established as safe, while allowing for a reliable measurement of pain tolerance and pain intensity (Mariano et al 2015, Mitchell et al 2004). Participants were not given any cues of the temperature of the water. The duration of submersion was collected with a stopwatch. Upon completing the CPT participants were asked to rate the level of discomfort experienced (on a 0-10 point Likert-scale, from none to extremely intense).

After each active or sham tDCS session a checklist of potential side-effects was used (Brunoni et al 2011). As suggested by Brunoni (2011), participants were instructed to describe any discomfort they may experience. The intensity of the acknowledged discomfort was rated by participants using a scale with a range of 0 to 3 points. Displayed in ascending levels, the scale measures the absence of a potential side-effect, and escalates in intensity (0 = Absent, 1 = Mild, 2 = Moderate, and 3 = Severe). The researcher administrating active or sham tDCS further evaluated each potential side effect endorsed by participants. Researchers ask the participant to indicate the degree to which they consider the discomfort to be related to tDCS through an escalating scale ranging from 0 to 4 points (0 = None, 1 = Remote, 2 = Possibly, 3 = Probable, and 4 = Definite). Additionally, the researcher also rated the degree to which he/she considers the discomfort to be related to tDCS using the same scale. See table 3. Given that there is evidence to suggest that participants can distinguish between active and sham tDCS (O'Connell et al., 2012) and this may result in an expectation effect, participants were formally assessed

after the last outcomes assessment about their perception of which arm of the study they were assigned.

Missed Sessions and Early Termination of Participation

Participants who for any reason miseds a scheduled brain stimulation session or assessment were given the opportunity to make up the session/assessment on the following day (including weekends as necessary). Participants were allowed to withdraw from the study for any reason without affecting their clinical care.

Data Management Procedures

Data quality was promoted by coding all paper or electronic documents. Paper charts and electronic data for each participant's assessments (e.g., tDCS potential side-effect checklist, cold presser test results, etc) were kept in a locked file cabinet at The Pain Management Program until the project staff enter the responses into the electronic database, which was secured on a Menninger Clinic server. After entry into the electronic database, paper charts of the assessments were destroyed via confidential recycling at The Menninger Clinic. To improve the privacy and security of electronically transmitted and physically collected data, a safety plan was established (Elhai & Frueh 2016). The Chronic Pain Tracker app offers a pattern lock security mechanism that prevents unauthorized access to the participant's data. A unique login id and password is required to access the computers used for research, the app and the iPad. Built-in encryption of the iPad device ensures no third party had access to the private database. Assessments completed through the iPad were transferred though a Wi-Fi Protected access to an external electronic database. Technical specifications protecting both the database for participant's information and iPad associated database are protected with a firewall option built into The Menninger Clinic's server.

Usual Care in the Pain Management Program

All participants took part within the Pain Management Program's centralized ("one-stop shopping") model of integrative inpatient clinical services with an expected length of stay of 5 weeks. Diagnosis of CP and pre-existing psychiatric disorders were reviewed by the Pain Management Program prior to admission. Patients received comprehensive psychiatric and medical evaluation as well as personalized treatment. Components of the psychiatric care typically included pharmacologic optimization, including detoxification from opiates and/or other addictive medications as indicated and tolerated. Additionally, given the extended length of the hospitalization, adequate time in treatment allowed for evaluation of adverse polypharmacy, allowing for a reduction in the number, complexity, & dangerousness of patients' medication burden (Madan et al., 2015a). Further, psychotropic medication management targeting both psychiatric and pain symptoms was optimized via pharmacogenomics-informed medical decision based on known interactions between specific psychotropic medications and individually expressed alleles in various transporters, receptors, and enzymes as coded by genes (Madan et al., 2015b). A board-certified internist completed a comprehensive medical evaluation and continues to manage symptoms as indicated throughout the hospitalization. The evaluation included: a physical exam (i.e., skin exam; complete neurologic, cardiovascular and abdominal exams; focused exam of wounds; areas of pain; areas of concern as identified by the patient; and when indicated, pelvic and rectal exams); serum analysis (i.e., complete blood count; thyroid function panel; complete metabolic panel with magnesium and phosphorus; tests for sexually transmitted diseases; tests for vitamin deficiency;

tests of inflammatory biomarkers; and Westergren sedimentation rate (Madan et al., 2016). Of note, these interventions occurred within the context of 24-hour nursing care, resulting in near perfect compliance with prescribed regimen doses and close and objective monitoring of side effects.

While medical management of patients was a core feature of the Pain Management Program, psychological assessment and psychotherapeutic care were essential components of the daily treatment schedule. Personality and neuropsychological testing were conducted during the initial weeks of the hospitalization, including pain specific measurement. A multi-theoretical conceptualization was used to integrate evidence-based treatment for CP, including cognitive-behavioral therapy (CBT; (Åkerblom et al 2015, Turner et al 2007, Williams et al 2012), acceptance and commitment therapy (ACT; (Hann & McCracken 2014, McCracken & Vowles 2014, Vowles et al 2014), mindfulness-based therapeutic approaches (Howarth et al 2016, Veehof et al 2011, Zeidan et al 2012), and motivational enhancement therapy (Aguerre et al 2015, Alperstein & Sharpe 2016). There was concerted attention to the behavioral facets of individual pain experiences, including 1) completing a functional analysis (i.e., antecedents and reinforcing contingency of pain-related behaviors); 2) introducing behavioral strategies to help reduce autonomic hyperarousal commonly observed among CP patients (e.g., diaphragmatic breathing, progressive muscle relaxation, guided imagery, self-hypnosis); and 3) facilitating values-based behavioral activation. Skin conductance biofeedback was introduced, and practice was encouraged on a daily basis. The systemic-constructivist conceptualization provided opportunities for family interventions, education and counseling, as well as assistance with discharge planning. Participation in instructor-lead, low-impact physical exercise, including yoga, was strongly encouraged. Dietary consultation, physical/aqua therapy, and chaplaincy services were integrated into treatment plans as indicated. Again, 24-hour nursing care allowed self-management support for CP. All treatment occurred within the context of a therapeutic milieu, including patient governance with ample opportunity for spontaneous for patient interaction, especially during meals.

Finally, real-time standardized outcome assessments were completed by each inpatient during admission, every two weeks during the hospitalization as well as upon discharge (Allen et al 2009, Confer et al 2015). The outcomes assessment protocol included standardized measures of psychopathology, functioning and wellbeing. All of the selected measures are used in clinical practice and research settings; each has sound psychometric properties with adequate sensitive to change. Patients and clinicians were provided reports of the assessments within 24 hours of completing them. Ongoing assessment of treatment outcomes allowed for modification of treatment plans (including adjustments to pharmacologic regimens), thus allowing for personalization of evidence-based treatments and improving the likelihood of treatment response.

Statistical Analyses

Statistical analysis were to be conducted using a 2X12 [tDCS group X time] mixed generalized linear modeling approach with CPT duration of submersion as the primary dependent measures. Secondary analysis were to employ hierarchical linear modeling (HLM) to examine changes in numerical ratings of self-reported pain, activity, and sleep disturbance, while controlling for mood (time-series). Had any of the outcome variables been non-normally distributed, each were to be log-transformed before applying the formal linear modeling analyses. All analyses were to be conducted using SAS/STAT software, Version 9.3 of the SAS System for Microsoft Windows, Cary, NC, USA.

Note, no formal analyses were conducted. Given the premature termination of the clinical program, the limited sample size of participants completing the study, the heterogeneity of CP etiology and psychiatric comorbidity among participants, as well as variable and personalized interventions delivered as a part of the clinical care participants received, the data collected would have been grossly underpowered to provide meaningful results.