INVESTIGATION AND MODULATION OF THE MU-OPIOID MECHANISMS IN MIGRAINE (IN VIVO)

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NINDS Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this *trial/study* will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations.

Site Investigator

Signed: _____ Date: _____

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LIST OF ABBREVIATIONS

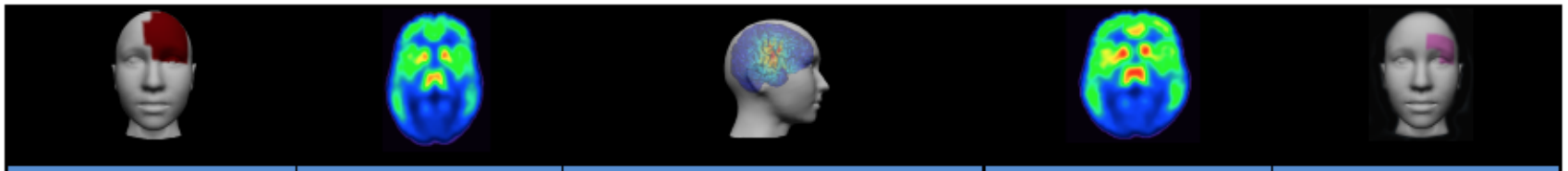
AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DHHS	Department of Health and Human Services
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
JAMA	Journal of the American Medical Association
JADA	Journal of the American Dental Association
MedDRA®	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UM	University of Michigan
UMHS	University of Michigan Health System
US	United States

PROTOCOL SUMMARY

Title:	Investigation and Modulation of the Mu-Opioid Mechanisms in Migraine (In Vivo)
Précis:	This is a phase 2, single center, three-arm, double-masked, randomized investigation and modulation of the μ-opioid mechanisms in migraine (in vivo). We will enroll 60 patients with episodic migraine (30 for the active M1 HD-tDCS group and 30 for the sham group). In addition, we will use the data from up to 10 healthy controls who were recruited and scanned during the NINDS-K23062946 project (IRBMED #HUM00027383; Dr. Alexandre DaSilva, Principal Investigator). We will then recruit healthy volunteers to a total of 30 age- and gender-matched healthy subjects. Each participant will undergo the sequence of events and evaluations laid out in the Schematic of Study Design (page viii), which will take approximately 3 months. Completion of full protocol enrollment and participation is expected to take approximately 5 years. Data will be collected on paper or electronic CRFs, or electronically on local systems (PET, MRI, QST), then transferred via HIPAA-compliant methods within the UMHS system for analysis by study staff.
Objectives:	To demonstrate that clinical and experimental pain measures in migraine patients are associated with μOR BP_{ND} in the thalamus and other pain-related regions, even during interictal phase (non-headache phase). To determine whether 10 daily sessions of M1 HD-tDCS have modulatory effect on clinical and experimental pain measures in migraine patients. To investigate whether repetitive active M1 modulation induces/reverts thalamic μOR BP_{ND}, and whether those changes are associated with clinical and experimental pain measures in migraine patients.
Population:	60 Patients age 18-65 years (inclusive) with episodic migraine (ICHD-3-beta); AND 30 age and gender matched healthy subjects Subjects will be recruited from the UMClinicalStudies.org database, the clinics at the University of Michigan (UM), and from other clinics in the region
Phase:	2
Number of Sites:	1
Study Duration:	5 YRS

Subject Participation Duration:	Approximately 3 Months
Description of Agent or Intervention:	High-definition transcranial direct current stimulation (HD-tDCS)
Estimated Time to Complete Enrollment:	4 Years

Schematic of Study Design I:



Screening Period	Week before daily M1 HD-tDCS sessions (Neuromodulation)	Active / Sham Neuromodulation (10 Daily Sessions) M-F x2		Week after daily M1 HD-tDCS sessions	Follow-up Period ⇒
First Appt	PET/MRI Sessions	5 Daily Sessions	5 Daily Sessions	PET/MRI Sessions	Follow-up at 1 Week and at 1 Month and 2 Months Following Neuromodulation

Schematic of Study Design II:

Timing **(Relative to Day 0)**	**Procedure**		
PreScreening (Up to 8 weeks prior to Day 0)	Phone Call: *IRB-Approved Prescreening Checklist/Script*		
Screening (Up to 3 weeks prior to Day 0)	Informed Consent Demographics History and Physical Exam Questionnaires Randomization, once subjects have been consented		
PET and MRI #1 (Up to 1 week prior to Day 0)	QST PET #1 Workup Questionnaires (PET-specific) Pregnancy Test and Drug Screen CFN (^{11}C-carfentanil) Injection MRI #1 Screening Form (MRI-specific) MRI Questionnaires*		
HD-tDCS x 10 Daily Sessions (Day 0 - 11; Week 1 and 2)	Migraine Active Questionnaires ≤2 mA current for **20 min/day** x 10 days (M-F over 2 wks) Questionnaires	Migraine Sham Control Questionnaires ≤2 mA current for **30 sec at start plus 30 sec at end** of session x 10 days (M-F over 2 wks) Questionnaires	* Healthy volunteers complete participation after PET/MRI #1 visit
PET and MRI #2 (Week 3)	QST PET #2 Workup Questionnaires Pregnancy Test and Drug Screen CFN (^{11}C-carfentanil) Injection MRI #2 Screening Form (MRI-specific) MRI Questionnaires		
Follow Up @ Week 1 (Week 3)	Questionnaires		
Follow Up @ Month 1 (Week 6)	Questionnaires		
Follow Up @ Month 2 (Week 10)	Questionnaires		

1. KEY ROLES

Individuals:	**Principal Investigator:** Alexandre F. DaSilva, DDS, DMedSc
Institutions:	**Program Official:** Michael L. Oshinsky

2. INTRODUCTION: Background Information And Scientific Rationale

2.1. BACKGROUND INFORMATION

Migraine is a debilitating chronic condition that affects most of the patient's existence, from childhood to late adulthood. During frequent headache attacks, its sufferers show marked increased sensitivity to noxious (hyperalgesia) and even non-noxious stimuli, a phenomenon called cutaneous allodynia that affects 63% of the patients (Bigal et al., 2008b). Although MRI-based techniques have provided insights into some brain mechanisms of migraine (Granziera et al., 2006; DaSilva et al., 2007a; DaSilva et al., 2007b), many questions regarding its molecular impact in the brain are still unanswered. The overall goal of this project is to provide a detailed understanding of the μ-opioid receptor mediated transmission in the brain of migraine patients, one of the most important central pain regulatory systems in humans, with the long-term objective of developing more focused neuromechanism-driven methods for migraine research and therapy.

2.2. RATIONALE

Preliminary studies from our NIH-NINDS K23 project using positron emission tomography (PET) with [11C] Carfentanil, a selective radiotracer for μ-opioid receptor (μOR), have indicated that there is a decrease in μOR availability (non-displaceable binding potential BP_{ND}) in the brain of migraine patients during the headache attacks and allodynia, including areas like thalamus and periaqueductal gray matter (PAG) (DaSilva et al., 2014a; DaSilva et al., 2014b; Nascimento et al., 2014). μOR BP_{ND} is an objective measurement in vivo of endogenous μ-opioid availability, and its acute reduction reflects the activation of this neurotransmitter system (Zubieta et al., 2001). This is arguably one of the neuromechanisms most centrally involved in pain regulation, affecting multiple elements of the pain experience (Zubieta et al., 2002). Moreover, MRI-based reports have found that those findings co-localize with neuroplastic changes in migraine patients (DaSilva et al., 2007a; DaSilva et al., 2007b). Conventional therapies are unable to selectively target those dysfunctional brain regions, and there is a paucity of data on how to reverse embedded neuroplastic molecular mechanisms when available medications and surgical therapies fail. Interestingly, several studies with motor cortex stimulation (MCS) have shown that epidural electrodes in the primary motor cortex (M1) are effective in providing analgesia in patients with refractory central pain (Lima and Fregni, 2008). The rationale for MCS stimulation is based in part on the thalamic dysfunction noticed in chronic pain and migraine (Lenz et al., 2004), and also on studies demonstrating that MCS significantly changes thalamic activity (Garcia-Larrea et al., 1999). Evidently, the invasive nature of such a procedure limits its indication to highly severe chronic pain disorders. New non-invasive brain neuromodulatory methods for M1, such as transcranial direct current stimulation (tDCS), can now safely modulate and activate the μOR system (DosSantos et al., 2012; DosSantos et al., 2014), providing relatively lasting pain relief in chronic pain patients and migraine (DaSilva et al., 2011c; DaSilva et al., 2011b)

(http://www.jove.com/details.php?id=2744). However, the electric fields generated by its most conventional analgesic montage are widely spread across the brain, lacking specificity on the pain-related structures directly targeted. Recently, a novel high-definition tDCS (HD-tDCS) montage (Villamar et al., 2013) created by our group was able to reduce exclusively “contralateral” sensory-discrimative clinical pain measures (pain intensity/area) in chronic patients by targeting more precisely the putative M1 region.

2.3. POTENTIAL RISKS AND BENEFITS

2.3.1. POTENTIAL RISKS

All supplies used are sterile and disposable. Subjects will not be identified in any reports on this study. In the case of adverse events or physical injury resulting from participation in this study, subjects are provided with contact numbers for the responsible physicians and a 24-hour emergency access number to obtain immediate medical care. Records will be kept confidential to the extent provided by Federal, State, and local law. Nevertheless, subjects are informed that the sponsor and the Institutional Review Board for the use of human subjects in research may inspect the records of this investigation. Experienced personnel using the standard safety procedures employed in clinical practice will perform the catheter insertions. These include the wearing of protective gloves, use of disposable materials and medication-grade solutions. The insertion of intravenous catheters is performed by skilled personnel, including the study physicians, research nurses and nuclear medicine technology staff. In over several years of practice, we have encountered no serious complications from intravenous cannulations. In the very unlikely event of vascular damage, medical or surgical treatment will be employed to minimize vascular injury. Infection at the site of cannulation will be treated with appropriate systemic antibiotic therapy or with surgical intervention. Idiosyncratic responses to the study radiopharmaceuticals are unlikely at the tracer doses employed, however, we will exclude subjects with prior history of allergic response to the study tracers, or chemically related drugs. A "crash cart" is immediately available in the PET suite, containing necessary drugs for management of allergic or other drug reactions. A physician is immediately available in the PET suite or in the immediately adjoining Nuclear Medicine Clinic area at all times when research subjects are present. The low-level radiation exposure arising from participation in the studies in this project is well within Federal guidelines established for participation of normal adult volunteers in medical research involving radiation. All subjects will be encouraged to drink plenty of fluids after the studies to encourage voiding and further diminish radiation exposure to the urinary tract and kidneys. During the performance of the studies, the volunteers will be monitored at all times by research personnel associated with the project (research coordinator, research assistants, radiology technologists) or the investigator. All volunteers will be provided the phone numbers for the Principal Investigator and the Research Coordinator in the consent form. A copy of the consent form is provided to each subject, who will be encouraged to contact the investigator if they notice any unusual symptoms or untoward side effects. The investigator has ample prior experience in the utilization of these procedures.

HD-tDCS

Transcranial Direct Current Stimulation (tDCS) is a safe technique that poses a non-significant risk to participants. The safety of this technique has been addressed and tested by multiple researchers (e.g., (Nitsche, Fricke et al. 2003; Nitsche, Liebetanz et al. 2003; Nitsche, Liebetanz et al. 2003; Priori 2003; Nitsche, Niehaus et al. 2004; Hummel and Cohen 2005; Iyer, Mattu et al. 2005; Fregni, Boggio et al. 2006)) who have concluded that tDCS, as applied in a manner similar to our proposed protocol, induces only temporary cognitive/motor effects, and no negative side effects. More than 30 research studies involving hundreds of participants have been published using tDCS. Hundreds more participants have undergone tDCS for unpublished pilot research (Nitsche, Liebetanz et al. 2003). No undesirable or long- lasting effects have been reported, nor have any participants reportedly abandoned a study due to discomfort. Researchers at the National Institute of Neurological Disorders and Stroke (NINDS)(Iyer, Mattu et al. 2005) conducted a safety study on our tDCS protocol, investigating 20minute sessions of 1 mA and 2 mA current stimulation with healthy controls (n=103). No negative effects were identified. Nitsche and colleagues (2004) found no measurable structural changes in brain tissue due to tDCS (Nitsche, Niehaus et al. 2004). Additionally, other studies (Fregni, Boggio et al. 2005; Hummel and Cohen 2005) have shown that tDCS can be used safely in stroke patients and in patients with major depression (Fregni, Boggio et al. 2006; Boggio, Rigonatti et al. 2007). In these studies only mild adverse effects, such as mild headache, have been reported. Finally, two recent studies showed that several sessions of tDCS are safe to be used in chronic pain syndromes, including one from our group in migraine (DaSilva et al. 2012), fibromyalgia and spinal cord injury (Fregni, Gimenes et al. 2006, Fregni, Boggio et al. 2006). Thus, a growing body of research from different laboratories has shown that tDCS is a safe, noninvasive, and painless technique for modulating neural excitability, with measurable but only transient effects. The protocol described in our study uses stimulation levels that fall well within safety limits established by basic research investigating neural tissue damage, as well as numerous studies applying (HD)-tDCS with human participants (Yuen, Agnew et al. 1981; McCreery, Agnew et al. 1990; McCreery, Agnew et al. 1990; Nitsche, Liebetanz et al. 2003). For more safety information on (HD) tDCS please see the following links:

tDCS (http://www.jove.com/details.php?id=2744) [DaSilva et al., 2011a]

and

HD-tDCS (http://www.jove.com/video/50309/technique-considerations-use-4x1-ring-high-definitiontranscranial) [Villamar et al., 2013]

PET

Potential risks to the subjects participating in these studies include those associated with MR and PET imaging. Prior to inclusion in the study, the presence of potential MR

risks, such as pacemakers, surgical clips or metallic surgical devices will be excluded by medical and surgical history using a standard review form. Potential PET risks include potential complications or inconveniences associated with venous cannulation, the administration of study radiopharmaceuticals, and the exposure to low level radiation. The radiation exposure resulting from these studies is well within that associated with routine radiological procedures and is not associated with adverse health consequences.

A 15 mCi injection of [11C]CFN will result in a whole body effective dose equivalent of 0.26 rem, which is less than 6% of the dose that occupationally exposed individuals are permitted to receive each year, and a critical organ (liver) mean dose equivalent of 0.89 rem. Completion of the maximum number of PET scans (four) will result in a whole body dose equivalent of 1.82 rem, which is 36% of the dose that occupationally exposed individuals are permitted to receive each year.

The proposed PET methods have no alternatives for collection of the necessary data at the present time. There are no serious risks associated with the intramuscular infusion of the salt solution. A known risk includes the possibility of puncturing a blood vessel.

QUANTITATIVE SENSORY TESTING

For both migraine subjects and healthy volunteers, thermal quantitative sensory testing will be performed in four areas: the right and left supraorbital area (temple), and dorsum of the hands.

We will use a standard clinical evaluation program designed for the Pathway system (MEDOC-Israel). This program is comprised of a series of hot and cold stimuli that are delivered from a baseline temperature of 32°C, bilaterally. The subject will control the heating/cooling unit with a computer mouse. They will be instructed to tap the mouse button at the first perception of pain. Each stimulus (hot and cold) will be delivered three times in each location, and the Pathway program records the average temperature.

This stimulus, though it may feel mildly painful, does not produce any skin damage. The QST is not associated with pain lasting beyond the study period nor with any irreversible damage to the body.

Infusion/Blood Collection

Puncturing of a blood vessel results in bruising and can be accompanied by minor swelling and pain. The condition is treated by icing and typically resolves in a few days. According to our records, since 1989, puncturing of a blood vessel occurred in two of more than 600 infusions.

Subjects may feel a slight needle prick when blood is drawn. Some patients may have a slight bruise that will go away within a few days. Sometimes, patients feel light headed

or feel dizzy. Other rare complications associated with the blood sample collection include:

• Infections

• Nerve lesions

• Accidental arterial puncture (when the needle pierces an artery instead of a vein).

Genetic Research/Confidentiality

Genetic research may provide information about who is at risk to develop the disease. Some people may find this information stressful or uncomfortable. While our research is focused primarily on pain mechanisms through new genetic technologies that allow us to look at all of the information across the genome, we may learn information about subjects regarding diseases not related to pain. We do not intend to release the results of the genetic testing to subjects.

If multiple members of a family are enrolled in research, information from this research may identify previously undisclosed biological relationships (i.e. non-paternity or non-maternity).

It is unlikely, but there is a possible risk of breach of confidentiality. The databases developed for this project will not contain information that is traditionally used to identify subjects, such as name, address, telephone number, or social security number. It is also possible that there could be violations to the security of the computer systems used to store the codes linking genetic and medical information to subjects. These codes will be maintained only at the University of Michigan.

2.3.2. KNOWN POTENTIAL BENEFITS

Participation in this study may help determine whether molecular mechanisms and their modulation are in effect to suppress pain in patients suffering from episodic migraine. Direct and longterm benefits to the subjects participating in the studies are not anticipated. Subjects will be informed that the medical significance of these studies is presently unknown, and that the results will not influence their subsequent medical care.

3. OBJECTIVES

3.1. STUDY OBJECTIVES

Objective #1:

To demonstrate that clinical and experimental pain measures in migraine patients are associated with μOR BPND in the thalamus and other pain-related regions, even during interictal phase (non-headache phase).

Objective #2:

To determine whether 10 daily sessions of M1 HD-tDCS have modulatory effect on clinical and experimental pain measures in migraine patients.

Objective #3:

To investigate whether repetitive active M1 modulation induces/reverts thalamic μOR BPND, and whether those changes are associated with clinical and experimental pain measures in migraine patients.

3.2. STUDY OUTCOME MEASURES

3.3. PRIMARY OUTCOME MEASURES

We hypothesize that migraine patients will have a reduction in thalamic μOR BP_{ND} at the baseline level (see preliminary data). The activation of μOR neurotransmission, calculated as reduction in μOR BP_{ND} during a sustained thermal pain threshold stress challenge will also be lower than in controls, and that both these measures will be associated with clinical and experimental pain ratings.

3.4. SECONDARY OUTCOME MEASURES

Our hypothesis is that 10 daily sessions of active M1 HD-tDCS modulation will induce analgesic after-effect in clinical and experimental pain measures. The focused targeting of M1 with HD-tDCS will lead to precise sensory-discriminative modulation of pain (area and intensity). This will be evidenced in our questionnaires, tracking tools, and quantitative sensory tests.

We hypothesize that after 10 M1 HD-tDCS sessions there will be an increase in μOR BP_{ND} (return toward healthy control values) in the thalamus and other pain-related brain areas in migraineurs at follow up, along with reductions in clinical/experimental pain measures.

4. STUDY DESIGN

This is a phase 2, single center, three-arm, double-masked, randomized investigation of the modulation of the μ-opioid mechanisms in episodic migraine (in vivo).

The population for the study will consist of 60 patients with episodic migraine (30 for the active M1 HD-tDCS group and 30 for the placebo HD-tDCS group). In addition, we will use the data from up to 10 healthy controls who were recruited and scanned during the NINDS-K23062946 project (IRBMED #HUM00027383; Dr. Alexandre DaSilva, Principal Investigator). We will then recruit healthy volunteers to a total of 30 age- and gender-matched healthy subjects.

All subjects will be enrolled as either episodic migraine or healthy volunteers (HV; N=90); if episodic migraine (n=60), they will be randomized to one of two treatment arms: active (n=30) or sham (n=30).

Each participant will undergo the sequence of events and evaluations laid out in the Schematics of Study Design (Protocol Summary; pages vii-viii), which will take approximately 3 months. Completion of full protocol enrollment and participation is expected to take approximately 5 years.

Data will be collected either on paper or electronic CRFs (most questionnaires, screening/demographic and logistical information regarding assessments) or electronically on local systems(PET, MRI, HD-tDCS), then transferred via HIPAA-compliant methods within the UMHS system for analysis by study staff.

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. SUBJECT INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Provide signed and dated informed consent form
- Willing to comply with all study procedures and be available for the duration of the study
- Male or female, aged 18 to 65, inclusive, and
- Meet criteria for an "episodic migraine" patient:
    - Episodic migraine (ICHD-3-beta) with at least one attack per month and less than 15 attacks per month
    - Migraine for at least 6 months
    - No intake of opiate medication for the past six months
    - No overuse of analgesic medication, defined as regular intake on ≥15 days per month for more than 3 months
    - Willing to limit the introduction of new treatments for headache management

OR

- Meet criteria as a Healthy Volunteer:
    - Without medication overuse
    - Without self-reported history of systemic disorders or other pain disorders, including migraine.

5.2. SUBJECT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

- Presence of any other systemic or chronic pain disorder
- History or current evidence of a psychotic disorder (e.g. schizophrenia) or substance abuse; bipolar or severe major depression, as evidenced by Beck Depression score of ≥ 20*
- Prior use of tDCS
- Ongoing, unresolved disability litigation
- History of neurological disorder (e.g. epilepsy, stroke, neuropathy, neuropathic pain)
- Current use of opioid pain medications
- Allergic response to study radiotracers or chemically-related drugs
- Excluded by MRI Center or PET Center safety screening checklist (as administered by study staff)
- Female participants who are pregnant, nursing, or planning a pregnancy, or who are of childbearing potential and are not using a reliable means of contraception during the baseline and study periods (negative urine pregnancy test must be available before any procedures are initiated)
- Treatment with an investigational drug, device or other intervention within 30 days of study enrollment (Screening Visit).
- Anything that would place the individual at increased risk or preclude the individual's full compliance with or completion of the study (eg, medical condition, laboratory finding, physical exam finding, logistical complication).

* The Beck Depression Inventory will be graded by study staff at the time of completion. Individuals with a score of ≥ 30 will be provided with a pamphlet from the Michigan Depression Center that contains information and contacts regarding depression. In addition, those individuals who respond to question #9 with answers #2 or #3, will be provided with a flyer from the Department of Health and Human Services National Suicide Prevention Lifeline (800 number and website).

5.3. STRATEGIES FOR RECRUITMENT AND RETENTION

We will recruit 60 episodic migraine patients divided into 2 groups: 30 for the active M1 HD-tDCS group and 30 for the placebo HD-tDCS group. In addition, we will use the data from up to 10 healthy controls who were recruited and scanned during the NINDS-K23062946 project (IRBMED #HUM00027383; Dr. Alexandre DaSilva, Principal Investigator). We will then recruit healthy volunteers to a total of 30 age- and gender-matched healthy subjects.

Recruited patients will be screened from the UMClinicalStudies.org (formerly Engage) recruitment network and the University of Michigan. In addition to active referral from pain centers, advertisements will be placed in other pain clinics in the region. In-hospital advertisements will also be placed in pain clinics and departments at the institution, as well as across the university.

Subjects recruited will be prescreened by phone using an initial IRB-approved questionnaire. Those who pass the phone screening will be scheduled for an in-person Screening Visit, which will commence with a verbal and written informed consent process. Once informed consent has been obtained, subjects will undergo further screening by obtaining a history and performing a physical exam and QST. Those subjects who are determined to be eligible to enter the study will be enrolled into either the migraine or healthy volunteer pools; if migraine, they will be randomized to active or sham treatment.

Study duration per subject is expected to be less than 3 months; however due to the scheduling of PET and MRI visits, visit reminders (eg, phone and/or email; subject preference) may be implemented to help with retention.

During the course of participation, subjects will be compensated according to amounts stated in the informed consent form and approved by the IRB.

5.4. TREATMENT ASSIGNMENT PROCEDURES

5.4.1. RANDOMIZATION PROCEDURES

Participants initially will be screened by phone. After clinical exam and diagnosis of episodic migraine (confirmed by IHS/ICHD-3-beta criteria) participants will be randomized to the treatment HD-tDCS or sham groups using the Taves covariate adaptive randomization method. Using this method, a new participant will be sequentially assigned to a group based upon the previous assignments of other participants and certain covariates. The first eight migraine participants will be randomized by coin flip and the remaining migraine participants will be randomized by age and gender, following the Taves covariate adaptive randomization protocol. Healthy volunteers will be age- and gender-matched to the earlier enrolled participants.

5.4.2. MASKING PROCEDURES

The PI, Co-Investigator, and any members of the research staff who will be analyzing study data will be masked to participant treatment. The Research Coordinator and any study staff who will be involved in the treatment of the study participants on the HD-tDCS study days will be unmasked.

5.5. REASONS FOR WITHDRAWAL

Subjects are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study subject's participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.6. HANDLING OF WITHDRAWALS

Subjects wishing to withdraw from the study at any time may notify the study team.

5.7. TERMINATION OF STUDY

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the Principal Investigator and NIH-NINDS. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

6. STUDY INTERVENTION

6.1. STUDY PROCEDURAL INTERVENTION(S) DESCRIPTION

We will conduct a single-center, sham-controlled, double-blinded study to prospectively investigate the neuromodulatory effects of M1 HD-tDCS in pain intensity and brain molecular neuroplasticity in a cohort of episodic migraine patients. The subjects will participate in 10 daily sessions (eg, Monday – Friday for two weeks), either active or sham M1 HD-tDCS.

6.2. ADMINISTRATION OF PROCEDURAL INTERVENTION

In the active HD-tDCS group, stimulation will be applied for 20 minutes. For sham-controlled tDCS sessions current will be applied only for 30 seconds at the beginning and 30 seconds at the end of each 20-minute session, as sensations arising from tDCS treatment occur mostly at the beginning and end of application. Nonetheless, groups will be composed of tDCS-naïve patients to avoid comparison between sham and active from ongoing and previous experiences.

These HD-tDCS sessions will be conducted by study staff trained in the technique by the PI. Sessions will occur at the University of Michigan Hospital Systems (UMHS); hence, a licensed physician will be available by pager at all times.

6.3. PROCEDURES FOR TRAINING OF CLINICIANS ON PROCEDURAL INTERVENTION

All study clinicians will be trained in HD-tDCS technique by the PI (or trained designee) according to the study Manual of Procedures (MOP).

6.4. ASSESSMENT OF CLINICIAN AND/OR SUBJECT COMPLIANCE WITH STUDY PROCEDURAL INTERVENTION

Study staff performing each procedural administration will be trained in a standardized manner so as to assure compliance with the protocol. Likewise, the participation of study staff in subject scheduling will assist in their compliance with study procedures and instructions.

7. STUDY SCHEDULE

See Appendix A for a Schedule of Events.

7.1. PHONE PRESCREENING (DAY -56 TO -22)

Phone prescreening will take place for up to 8 weeks prior to Screening, to allow for scheduling of the Screening visits

7.2. SCREENING (DAY -21 TO DAY -1)

Screening will ideally take place during the week prior to the initial PET and MRI scans. The three-week window allows for scheduling of the PET and MRI visits up to three weeks following the Screening visit.

7.3. INTERMEDIATE VISITS

PET #1 (Day -21 to Day -1)

The PET scan will ideally take place during the week prior to the initial HD-tDCS session. The 21 day window allows for scheduling of the PET and MRI visits within three weeks of each other.

MRI #1 (Day -21 to Day -1)

The MRI will ideally take place during the week prior to the initial HD-tDCS session. The 21 day window allows for scheduling of the PET and MRI visits within three weeks of each other.

HD-tDCS #1-10, Day 0-4 and 7-11[1]

On DAY 0, HD-tDCS will begin. Subjects will have been randomized prior to Day 0, but after consent has been provided.

PET #2 (Day 16 ± 2)

PET Scan #2 will take place during the week following HD-tDCS. If it cannot be scheduled during this week, it may be completed during the following week.

MRI #2 (Day 16 ± 2)

MRI #2 will take place during the week following HD-tDCS. If it cannot be scheduled during this week, it may be completed during the following week.

[1] M-F; missed days can be doubled within (M-F) x 2 schedule and with study team approval

7.4. FOLLOW-UP VISITS

Follow-up visits will consist of adverse event collection, review of concomitant medications, and the completion of questionnaires. All follow-up visit dates are calculated relative to the HD-tDCS visits. The Week 1 visit may be combined with either the PET #2 or MRI #2 visit.

Follow Up Week 1 (Day 37 ± 2)

Follow Up Month 1 (Day 37 ± 2)

7.5. FINAL STUDY VISIT

Follow Up Month 2 (Day 65 ± 2)

The final visit will consist of adverse event collection, review of concomitant medications, the completion of questionnaires, and – if applicable – instructions regarding the follow-up of ongoing adverse events.

7.6. EARLY TERMINATION VISIT

If a subject terminates the study early for one of the reasons listed in Section 5.5 or 5.6, and is willing to return to the site for a final study visit, the following will be completed:

- Record adverse events as reported by subject or observed by investigator
- Provide final instructions to subject (e.g., follow-up of ongoing adverse events)

If the subject can not be reached or is not willing to return to the study site for a final study visit, the subject will be considered lost to follow up.

7.7. UNSCHEDULED VISIT

If a subject returns to the study site on a date that is significantly outside a visit window, the following assessments will be completed:

- Record adverse events as reported by subject or observed by investigator.

8. STUDY PROCEDURES/EVALUATIONS

8.1. CLINICAL EVALUATIONS

8.1.1. QUANTITATIVE SENSORY TEST (QST)

QST will be performed in four areas: right and left superficial masseter muscle, and dorsum of the hands.

Thermal stimulation: We will use a standard clinical evaluation program designed for the Pathway system (MEDOC Israel). This program is comprised of a series of hot and cold stimuli that are delivered from a baseline temperature of 32°C bilaterally. Subjects will control the heating/cooling unit with a computer mouse and they will be instructed to tap the mouse button at the first perception of pain. Each stimulus (hot and cold) will be delivered three times in each location, and the program records the average temperature.

Algometry: We will use an algometer (Somedic, Sweden) to define pressure pain threshold and tolerance in the four regions bilaterally, and in a randomized fashion. Each area will be evaluated three times, and the ultimate pressure pain threshold and tolerance levels will be the average of the three measurements recorded.

8.1.2. SUSTAINED THERMAL PAIN THRESHOLD STRESS (STPTS) PET CHALLENGE

The STPTS challenge on the trigeminal (chin area) region was selected for various reasons, including technical elements related to receptor quantification PET methods (e.g., sustainability and stability over a sufficient amount of time so that receptor quantification can be obtained). In addition, this 20min challenge has psychophysical responses that closely mimic those reported by chronic pain patients, as opposed to briefer challenges, making it a perfect protocol to compare neuronal mechanisms of pain regulation in healthy controls and migraine patients. In fact, more than half of all migraine patients have allodynia, especially thermal as we demonstrated (Figure 9). . It is also ecologically consistent with the process under study: persistent pain (threshold) conditions are fluctuating in nature (Gorin et al., 1999). By utilizing this challenge we test the individual capacity to mobilize neurotransmitters involved in responses to the STPTS challenge. Multiple heat trials occur at constant rates (1°C/sec ascending) from a starting baseline of 32°C, the intensity of which is controlled by the individual's experience. Subjects will be instructed to tap the mouse button at the first perception of pain to return temperature to baseline level. In that manner, individuals with migraine will select their heat thermal pain threshold based on the current sensitivity, avoiding unnecessary discomfort during the experiment. Receptor binding measures require the utilization of challenges sufficiently long in duration so that a constant state can be achieved and enough data points are collected to permit quantification. If lapses of attention occur during the 20min and the patient misses the threshold, invariably he/she goes back on track for the following trial due to the brief peak of painful experience. Our

PET challenge has successfully demonstrated significant average differences in heat pain threshold levels and μOR activation between ictal and interictal migraine phases. Most pain models do not have these characteristics because pain thresholds change over time, as the stimulus does not adapt to the progressive or faulty activation of descending anti-nociceptive mechanisms.

Figure 9. Sustained Thermal Pain Threshold Stress Challenge. Our adjustable PET apparatus, developed in house, provides a comfort contact of the probe on the patient trigeminal area for proper performance of the heat threshold trials.

8.1.3. MOLECULAR NEUROIMAGING MEASURE (TABLE 1)

PET Protocol	Early Phase [11C] Carfentanil 5-40min	Late Phase [11C] Carfentanil 45-90min
Migraine Active Group	Baseline	STPTS Challenge 20min
Migraine Sham Group	Baseline	STPTS Challenge 20min
Healthy Control Group	Baseline	STPTS Challenge 20min

PET Session: PET scans will be acquired with a Siemens HR+ scanner in 3-D mode (reconstructed FWHM resolution ~5.5mm in-plane/5.0mm axially) with septa retracted and scatter correction. Subjects will be positioned in the PET scanner gantry and two intravenous (antecubital) lines placed.

Receptor BP Measurements: [11C]carfentanil (CFN), a selective and specific μ-opioid receptor radioligand, is synthesized at high specific activity (> 2000 Ci/mmol) by the reaction of 11C-methyl triflate with desmethyl carfentanil as previously described. 15±1 mCi are administered to each subject with a maximum mass injection of 0.03 μg/kg to ensure that the compound is administered in true tracer quantities, eliminating significant receptor occupancy. The percent occupancy of μ-opioid receptors at peak

regional carfentanil concentrations has been calculated at 0.2%-0.6% by utilizing the average mass of carfentanil administered and the known concentration of μ-opioid receptors in the postmortem human brain. Fifty percent of the [11C]CFN dose will be administered as a bolus, and the remainder will be administered as a continuous infusion by using a computer-controlled automated pump to achieve steady-states between specific and non-specific binding regions (5-7 minutes post-tracer administration with Logan plots, and full equilibrium conditions and Logan plots at 40 minutes post-tracer administration) for baseline (resting-state) and 20min of STPTS challenge for μ-opioid system activation analysis. Twenty-eight frames will be acquired over 90min.

Subsequently, dynamic image data for each of the receptor scans are transformed on a voxel-by-voxel basis into three sets of parametric maps, which are co-registered to each other. These are (1) a tracer transport measure (K1 ratio, proportional to cerebral blood flow; tracer transport=blood flow x tracer extraction) and receptor-related measures (non-displaceable binding potential, BP_{ND}), encompassing data from (2) 10-40 min (baselines) and (3) 45-90 post tracer administration (pain or control). These parametric images are calculated using a modified Logan graphical analysis (Logan et al., 1996) with the occipital cortex (a region devoid of μ-opioid receptors) as the reference region. The Logan plot becomes linear well within 10min after the start of radiotracer administrations with a slope proportional to the Bmax/Kd + 1 for this receptor site. Bmax/Kd is the “receptor related” measure BP_{ND}.

Blood Collection: Each subject who has agreed to participate in the genetic analysis will have the blood drawn from their arm vein during the PET session(s). Blood will be collected from an intravenous line placed in the arm opposite that used for radiotracer administration.

The blood for the genetic analysis will be collected during each subject's PET scan(s) if they have indicated their interest in participating in the genetic analysis portion of the study. At the beginning of the PET scan(s), blood will be drawn for genetic and biomarker analysis (24 mL maximum). During the PET scan(s) ~6mL of blood will be drawn at twenty minute intervals starting at time 0 minutes. The total volume of blood per PET scan will not exceed 70 mL.

MRI Acquisition: While healthy controls will only undergo one 45min MRI scan, episodic migraine patients will undergo two identical 45min MRI sessions, the week before and the week following the 10 daily HD-tDCS sessions. Before and after the MRI scan(s) participants will complete the PANAS questionnaire.

MRI scans are acquired on a 3 T scanner (General Electric, Milwaukee, WI). These images provide anatomical information for structure identification and will be utilized for the anatomical standardization to the ICBM/MNI atlas coordinate system. This will establish the linear and non-linear warping transformation matrices to be applied to the co-registered receptor binding maps. The acquisition sequence is axial T1 FAST SPGR

MR (TE = 3.4, TR = 10.5, TI = 200, flip angle 25 deg, FOV 24cm, 1.5mm thick slices, NEX = 1), acquisition matrix 256x256, 60 slices. T1-weighted MR and PET images of each subject are then co-registered to each other using a mutual information algorithm (Meyer et al., 1997). For this purpose, K1 ratio images are first aligned to the MR, and the transformation matrix applied to the co-registered BPND scans of the same image set. The MR scans are then anatomically standardized to ICBM brain atlas stereotactic coordinates by non-linear warping, and the resulting transformation matrix applied to both K1 ratio and BPND image sets (Zubieta et al., 2001, 2002; Zubieta et al., 2003b; Zubieta et al., 2003a). As an alternative approach for Aim3, 1H-MRS spectra will be collected from the ACC (3x2x3cm) based on our prior work showing Glx alterations in this region following tDCS therapy. Single-voxel point resolved spectroscopy (PRESS)(TR/TE=2000/35ms) will be performed using 'VAPOR' water suppression with 32 averages to measure Glx and NAA levels. A MEGA-PRESS experiment, which edits out the overlapping creatine peak at 3.0ppm will measure GABA levels (Mescher et al., 1998). The MEGA-PRESS experiment will use: TE=68ms (TE1=15ms/TE2=53ms); TR=1.8s; 256 transients of 2k datapoints; spectral width=2kHz; frequency selective editing pulses (14ms) applied at 1.9ppm (ON) and 7.46ppm (OFF).

For the MRI and PET sessions, patients cannot experience a migraine attack within 48 hr prior to the scan. The morning of each scan one of the researchers will call the patient to confirm absence of a migraine in the past 48 hours. If a migraine has occurred, the scan will be rescheduled. If the scans cannot be scheduled for exactly the week before and after the tDCS sessions, they will be scheduled within 2 weeks of tDCS. Also, if an unexpected problem occurs during an MRI or PET, the subject will be asked to complete an additional scan.

8.1.4. TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS)

We will conduct a single-center, sham-controlled, single-blinded study to prospectively investigate the neuromodulatory effects of M1 HD-tDCS in pain intensity and brain molecular neuroplasticity in a cohort of episodic migraine patients. The patients will participate in 10 daily sessions—5 daily sessions each weekday for two consecutive weeks—of either active or sham M1 HD-tDCS. **(Figure 10)**. If a patient misses the day of a tDCS session, two tDCS sessions will occur the following day. tDCS sessions will be conducted at the University of Michigan Health System (eg, Michigan Clinical Research Center, Center for Human Growth and Development). Before and after each tDCS session patients will complete pain and mood questionnaires.

Prior to brain stimulation, the subject's scalp will be prepped in the M1 area contralateral to the subject's worst pain. The vertex will be found by measuring the midpoint between nasion and inion and the midpoint between the pre-auricular areas. Then the midpoint from the vertex to the pre-auricular point, on the side contralateral to the patient's worst pain, will be marked so that stimulation can be applied to the same spot each day. Alcohol pads will be used to wipe a 4 cm x 4 cm square centered over the motor cortex, followed by the application of approximately 6 mL of aloe vera gel to hydrate the scalp.

After 5 minutes have passed, the scalp will be wiped with gauze to remove excess gel. A perforated cloth cap with a chinstrap will then be placed on the head; this will secure plastic casings in the desired position of each electrode. Approximately 1 mL of Lectron II Conductivity Gel will be injected into each electrode casing slot. Four electrodes will be placed, with the upper anode placed on C3 and lower anode on C5, and the upper and lower cathodes placed anteriorly on FC3 and FC5, respectively, using the International Electroencephalography (EEG) 10-20 system (Zaghi et al., 2010). Approximately 1 mL of additional gel will be injected into the electrode casings. Ag/AgCl sintered ring electrodes with the rough surface directed towards the skin will be placed into the gel and held in place with plastic caps. The electrode wires will be held in place with a light adhesive tape (eg, Scotch tape), and the contact quality tested. Procedures will be reviewed with the subject before proceeding

In the active HD-tDCS group, ≤2 mA current stimulation will be applied for 20 min. For sham-controlled tDCS sessions current will be applied only for 30 sec - this is a frequent method of sham stimulation (Gandiga et al., 2006) as sensations arising from tDCS treatment occur mostly at the beginning and end of application. Nonetheless, groups will be composed by tDCS-naïve and different patients to avoid comparison between sham and active from ongoing and previous experiences.

tDCS has been used in a growing number of laboratories worldwide since 1984. Although mild adverse effects induced by (HD-)TDCS have been identified, they can be avoided if the safety guidelines are followed (Nitsche et al., 2003b). In addition to the baseline evaluation our examination will include: Patient Global Assessment, tDCS Side Effects Questionnaire, and Adverse Events Reporting. For more detailed information on the (HD-) tDCS protocols and safety use, please check the following links: tDCS (http://www.jove.com/details.php?id=2744) (DaSilva et al., 2011a) and HD-tDCS (http://www.jove.com/video/50309/technique-considerations-use-4x1-ring-high-definition-transcranial) (Villamar et al., 2013). Those peer-reviewed video-articles, created by our laboratory and collaborators, have been seen by more than 150,000 viewers and have been used as (HD)-tDCS tutorials by multiple academic centers and laboratories worldwide.

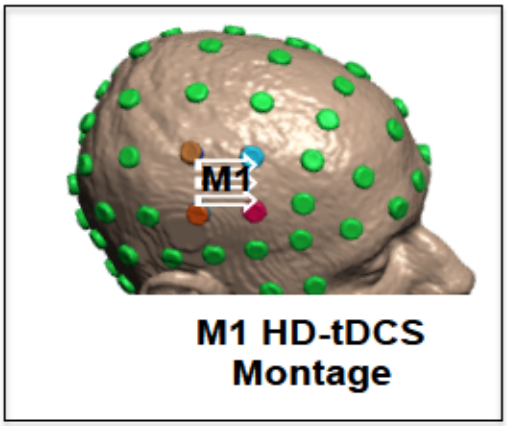


Figure 10. M1 HD-tDCS montage for homuncular head and facial region.

8.2. LABORATORY EVALUATIONS

8.2.1. CLINICAL LABORATORY EVALUATIONS

Pregnancy and drug screen testing will be performed by dipstick analysis.The results of each test will be immediately related to the subject and if positive, a repeat test may be performed on a second sample. These coded research results will be recorded in a file that is kept separately from the rest of the research data.

8.2.2. SPECIAL ASSAYS OR PROCEDURES

Serial blood samples for genetic analysis, not to exceed 70 mL per subject, will be collected during PET scanning. Details can be found in the Manual of Procedures.

8.2.3. SPECIMEN PREPARATION, HANDLING, AND SHIPPING

8.2.4. INSTRUCTIONS FOR SPECIMEN PREPARATION, HANDLING, AND STORAGE

Blood samples will be collected according to the schedule in Appendix A, and will be prepared, handled and stored following protocols set forth in the study Manual of Procedures.

8.2.5. SPECIMEN SHIPMENT

Samples will be stored on site until analysis.

9. ASSESSMENT OF SAFETY

Findings that are deemed grossly abnormal may be shared with the subject for further clinical evaluation by an outside physician. However, those findings generated in this study are not to be used for diagnostic purposes. In the same vein, interpretations of potential abnormal findings are not to be used for diagnostic purposes. The focus of this study is research, though this information may be shared in the best interest of the subject.

9.1. SPECIFICATION OF SAFETY PARAMETERS

Safety parameters for this study are comprised of the informed consent and screening processes, including the pregnancy dipstick test.

9.2. METHODS AND TIMING FOR ASSESSING, RECORDING, AND ANALYZING SAFETY PARAMETERS

9.2.1. ADVERSE EVENTS

An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

9.2.2. EXPECTED ADVERSE REACTIONS

Determination of whether a finding is clinically significant, expected AE will be made by the Principal Investigator or a Co-Investigator and will be documented on a CRF.

9.2.3. SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the

subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2.4. UNANTICIPATED PROBLEMS

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.2.5. PROCEDURES TO BE FOLLOWED IN THE EVENT OF ABNORMAL LABORATORY TEST VALUES OR ABNORMAL CLINICAL FINDINGS

Clinical laboratory values (other than pregnancy tests results) that are noted as abnormal and clinically significant at study exit and that are changes screening values will be documented as AEs.

9.3. REPORTING PROCEDURES

9.3.1. SERIOUS ADVERSE EVENTS

Serious adverse events will be reported to IRBMED according to institutional requirements.

9.3.2. REGULATORY REPORTING FOR STUDIES NOT CONDUCTED UNDER SPONSORED IND

Reports will be submitted to NIH-NINDS on the schedule as requested.

9.3.3. OTHER UNANTICIPATED PROBLEMS

Other unanticipated problems will be reported to IRBMED on a case-by-case basis.

9.3.4. REPORTING OF PREGNANCY

If a subject has a positive pregnancy test after signing informed consent, she will be informed of this result in a confidential manner by study staff. If she wishes, her primary care physician will be notified (with her documented consent). This will be reported as an “other unanticipated problem”.

9.4. SAFETY OVERSIGHT

The study will be monitored by the University of Michigan Institute for Clinical Health Research (MICHR). Adverse event/serious adverse event reporting will be to and ethics oversight will be completed by the University of Michigan Medical School IRB (IRBMED).

10. CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the Michigan Institute for Clinical and Health Research (MICHR). The monitor will evaluate study processes and documentation based on NINDS standards.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by MICHR. The CMP will specify the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Staff from MICHR will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the CMP. Documentation of monitoring activities and findings will be provided to the site study team, the study PIs, and the NINDS.

10.1. SITE MONITORING PLAN

The Site Monitoring Plan (SMP) will be developed by MICHR in conjunction with the site. The SMP is a listed supplemental document (see Supplemental Documents, Page 45). These documents are relevant to the protocol, but they are not considered part of the protocol.

11. STATISTICAL CONSIDERATIONS

The main contrasts of interest will be modeled using both volume-of-interest (VOI) data with SPSS *and* parametric statistical maps using the SPM8 package and a general linear model for the radiotracers. The main effect of interest [effect of acute and chronic pain, opioid and psychophysiological measures, before and after 10 M1 HD-tDCS sessions (active or sham) can be modeled by t-tests or ANOVA (e.g., effect of pain), or ANCOVA (with age as covariate), with post-hoc t-tests to determine the direction and magnitude of regional changes. However, a global model will also be utilized to determine the main effects of pain, and interactions with sex and other nuisance variables (e.g., age). In that manner, we will examine the main effects of migraine and repetitive M1 HD-tDCS neuromodulation on receptor BP_{ND}, BP_{ND} changes in the thalamus and other pain-related regions in response to an experimental pain challenge, interrelationships between variables, and additional interactions with covariates of interest and nuisance variables.

Two sets of analyses will be completed with the PET data: *Volume of Interest Analysis:* First, we will conduct a hypothesis-driven VOI analysis in which selected brain areas are examined. It offers the advantage of a relatively narrow search within the thalamus and other regions already known to be involved in the regulation of pain and in sex differences in these phenomena (e.g., anterior cingulate, insular cortex, nucleus accumbens, amygdala, periaqueductal gray for [^{11}C]carfentanil scans). Predefined VOIs obtained from the data acquired in previous studies (Zubieta et al., 2001; Scott et al., 2008) will be utilized for this purpose and applied to the functional image data in stereotactic space. The VOIs will then be transferred to the μ-opioid receptor BP_{ND} maps. *Statistical Parametric Mapping:* In subsequent analyses, statistical parametric maps will be obtained using whole brain image subtraction routines utilizing the images warped to stereotactic coordinates, as above. SPM analyses will be employed for the radiotracer, as shown in the Preliminary Data. Differences between conditions and subject groups will then be mapped into stereotactic space using *t*-maps of statistical significance and SPM8 and Matlab software, using a general linear model and correction for multiple comparisons (Friston et al., 1995). These maps are displayed superimposed over the anatomically standardized T1-weighted MRI of the subjects. This second analysis does not assume that specific regions are involved selectively, and a brain-wide search is performed on a voxel-by-voxel basis. Only gray matter pixels and regions with specific binding are included in the statistical parametric analyses (voxels with BP_{ND} values > 0.2) (Wager et al., 2007). For each subtraction analysis, one- or two-sample *t*-statistic values are calculated for each pixel using a pooled smoothed variance across voxels (Worsley et al., 1992). Areas of significant differences are detected using a statistical threshold that controls a Type-I error rate at $p = 0.05$ for multiple comparisons, which is estimated using the Euler characteristic (Worsley et al., 1992) based on the number of pixels in the gray matter and image smoothness (Friston et al., 1991). We will also use a multiple comparisons procedure that controls the false discovery rate (FDR; (Genovese et al., 2002), particularly in the case of preliminary analyses (years 2-3) that would not be fully powered for standard multiple comparisons

correction. The standard Euler characteristic method described above controls the Family-wise Type-I error rate for any false positives whatsoever.

11.1. STUDY HYPOTHESES

How are endogenous μ-opioid mechanisms affected in migraine patients?

Aim 1. To demonstrate that clinical and experimental pain measures in migraine patients are associated with μOR BP_{ND} in the thalamus and other pain-related regions, even during interictal phase (non-headache phase).

We hypothesize that migraine patients will have a reduction in μOR BP_{ND} at the baseline level. The activation of μOR neurotransmission, calculated as reduction in μOR BP_{ND} during a sustained thermal pain threshold stress challenge, will also be lower than in controls and both these measures will be associated with clinical and experimental pain ratings.

Feasibility: (Aim1) During the K23 NIH-NINDS award period, we evaluated *in vivo* the μ-opioid system during spontaneous episodic migraine headaches. Seven patients were scanned at interictal and ictal phases using the selective μ-opioid receptor (μOR) radiotracer [^{11}C]carfentanil (Figure 11). In the ictal phase there was dysfunctional μOR activation in the medial prefrontal cortex (mPFC), an area highly related to clinical pain processing. Furthermore, μ-opioid binding changes in mPFC showed moderate negative correlation with the combined extension and severity of the attacks. These results indicated for the first time the acute activation of the endogenous μ-opioid neurotransmission interacting with μOR due to the pain of the migraine attack (DaSilva et al., 2014a).

(Aim 1.2) When challenged for sustained thermal stimulus on the trigeminal ophthalmic region (STPTS) during the ictal and interictal phases, six of those migraineurs showed ictal allodynia that was concurrent and positively correlated with μOR activation in the midbrain, extending from red nucleus to vlPAG. These findings demonstrate for the first time *in vivo* the high μOR activation in the migraineurs' brains in response to their allodynic experience (Figure 12 & 13)(Nascimento et al., 2014b).

We then compared the migraineurs in the interictal phase with age and gender matched healthy controls. In our preliminary data we noticed lower μOR BP_{ND} in pain-related brain regions, especially the thalamus (Figure 14), at baseline (no stimulus) (Aim1.1) and during thermal stimulation (STPTS) (Aim1.2). <u>These results indicate that there is higher endogenous μ-opioid neurotransmission interacting with μOR in migraineurs, even during the interictal phase, either by the higher occupancy or loss of μ-opioid receptors available</u>.

Analysis: First, we will continue to examine differences in baseline μOR BP_{ND} and in the activation of μ-opioid neurotransmission in a large control sample of migraine patients to confirm our preliminary results. A mixed model of variance will be employed, accounting for age and other nuisance or potentially influencing variables (e.g., plasma levels of estradiol, proximity of attacks). Reductions in baseline μOR BP_{ND} and in the activation of μ-opioid neurotransmission in migraine compared to controls should be expected. Second, we will investigate individual associations between baseline μOR BP_{ND} levels and their change during the STPTS challenge in the thalamus, other pain-related regions, and acute and chronic pain measures, as well as between μOR BP_{ND} levels and pain frequency by means of pair-wise correlation coefficients. We intend to use either Pearson's version or the Spearman's rank version of the correlation coefficient depending on whether the variables investigated follow normal distribution or not. Subsequently, we shall investigate the joint effect of pain intensity and frequency on the μORBP_{ND} by means of a multiple linear regression analysis where μOR BP_{ND} is the outcome, and the other two are used as predictor clinical variables. The linear regression analysis allows us to identify the effect of either one on μOR BP_{ND} for a fixed level of the other predictor.

Potential pitfalls and alternative strategy: Regarding possible negative results we have to explore other scenarios: First, our hypothesis was wrong. However, this is unlikely due to extensive data from our group showing decreased levels of μOR BP_{ND} in chronic pain, including our initial migraine and allodynia data (DosSantos et al., 2012; DaSilva et al., 2014a; Nascimento et al., 2014a). Nonetheless, if the migraine mechanisms are not through a change in the μ-opioid system we need to explore alternative mechanisms in the future, such as the glutaminergic and GABA systems—data which will also be acquired during this study (see Aim3 alternative strategy)— hence, the results will still be interesting to report and investigate further. Second, μOR BP_{ND} levels at baseline will not be correlated with pain levels (also unlikely based on our data) (DaSilva et al., 2014a; DosSantos et al., 2014a). Although we are powered to perform all the analyses in this study, correlation analysis is a test that has low power. In the case of a statistical trend for a correlation, we will look at thalamus and other pain-related regions, and consider increasing the sample size by 20% and then describing these specific results as exploratory. We will also use different pain ratings (e.g., Pain*Trek*).

Does M1 HD-tDCS have modulatory effect on experimental and clinical measures in migraine?

Aim 2. To determine whether 10 daily sessions of M1 HD-tDCS have modulatory effect on clinical and experimental pain measures in migraine patients.

Our hypothesis is that 10 daily sessions of active M1 modulation, as compared to sham, will induce a greater analgesic after-effect in clinical and experimental pain measures. The focused targeting of M1 with HD-tDCS will lead to more precise sensory-discriminative modulation of pain (pain area and intensity). This will be evidenced in our

questionnaires (e.g., McGill, PANAS), pain tracking tools, and quantitative sensory tests.

Feasibility: (Aim 2.1) We preliminarily investigated the analgesic effects of M1-SO tDCS in chronic migraine (DaSilva et al., 2011c). Patients were randomized to receive 10-sessions of active or sham M1-SO tDCS for 20 min with 2 mA, one session every other day ("second-daily"). The primary outcome measure was pain intensity. There was a significant interaction term (time vs. group) for the main outcome (pain intensity) and also for length of migraine episodes (ANOVA, $p<0.05$). Post-hoc analysis showed a significant improvement in the follow-up period for both outcomes in the active tDCS group only. In addition, patients in the active group showed a significant improvement in the clinician global impression. Nonetheless, it is now better understood that daily applications, instead of second-daily, leads to greater and faster increases in analgesia; hence, the selection of 10 daily sessions in our current protocol instead of every other day (Alonzo et al., 2012). Our findings reinforce the evidence that migraine measures have a positive response to M1-SO tDCS. However, our results also show that significantly spread electric fields are generated, not only in M1, but also in the thalamus and other pain-matrix regions (Figure 15), making it harder to dissect the direct role of M1 modulation on pain measures (DaSilva et al., 2011c).

Feasibility: (Aim2.2) In order to evaluate the analgesic effect of focally targeted M1 modulation, we have developed a novel M1 HD-tDCS montage with 2 x 2 electrode design, which we tested on a cohort of patients with another chronic trigeminal pain illness, temporomandibular disorder (TMD). Our computational model simulated our montage's current flow through tissues captured with 3D imaging, accounting for the tissue type, tissue shape, tissue resistance, electrode positioning, and strength of the current. Greatest density was focused on the lower region of the precentral gyrus/sulcus, targeting the putative homuncular craniofacial M1 region and immediately within the HD-tDCS 2 x 2 electrodes (Figure 16). This is the region where invasive motor cortex stimulation produces maximal analgesic effect for head and facial pain (Nguyen et al., 1999). We screened 78 patients for this study, and of those 24 (30.8%) were randomized, with 12 per group. All patients completed the active or placebo 5-daily sessions of M1 HD-tDCS study according to the protocol. There were statistically significant between groups differences for sensorimotor measurements, including VAS 50% responders ($p=0.04$) at one-month follow-up (Table 2), pain free mouth opening at one-week follow-up ($p<0.01$), and most important: improvement of contralateral sensory-discriminative pain measures as collected by PainTrek (e.g., pain intensity, area and their summation), not ipsilateral pain measures, during the treatment week ($p<0.01$) (Table 3). In addition, we found "no" significant evidence that mood changes differed overall between the groups, as evaluated by the Positive and Negative Affect Scale (PANAS), indicating that our focused M1 HD-tDCS montage selectively modulated sensorimotor outcomes.

Potential pitfalls and alternative strategy: There is a possibility that at the end of the tDCS and PET study we get negative pain measures results. In this case, our 2nd

hypothesis was wrong, and only modulation of the pain-related neural networks will be seen in migraineurs (Aim3); however, this is unlikely based on previous successful experience with M1-tDCS and chronic migraine (DaSilva et al., 2011c), and experimental trigeminal pain (DosSantos et al., 2014b). A recent meta-analysis study in non-invasive M1 stimulation for chronic pain indicated an effective size of −0.86 (95% C.I., −1.54, −0.19) on the VAS (Zaghi et al., 2011). Another issue is the accuracy on targeting M1 in our montage. It is important to note that current can concentrate at distinct gyri/sulci sites so current flow, and thus brain activation, is not homogenous across an area of stimulation (Datta et al., 2009). Still, when external landmarks are used to target brain regions with HD-tDCS, computational models improve accuracy, but they are prediction models. In order to address this issue we will confirm the M1 location by using transcranial magnetic stimulation (Zaghi et al., 2010).

Feasibility: (Aim 3.1) We conducted analysis to demonstrate that tDCS can significantly modulate μ-opioid mechanisms and trigeminal pain measures in vivo, even immediately. This is a unique advance in pain translation research in humans, previously only possible in animal models. We examined with PET nine healthy volunteers with no history of chronic pain or systemic disorders. The protocol consisted of two PET scans, using [11C]carfentanil, a selective μOR radiotracer (Figure 17). The first PET provided a baseline evaluation of regional μOR BPND. During the second PET, placebo and active (2mA) M1-SO tDCS sessions were delivered sequentially, 20 min each, the same M1-SO tDCS montage as in our proposed migraine study. When analyzed separately, placebo and active tDCS were both associated with an acute reduction in μOR BPND, indicating activation of this neurotransmitter system in the PAG. In addition, the initial sham tDCS phase induced immediate activation of μORs in the left thalamus (Thal) and post-cingulate cortex, (PCC) and subsequently during the active tDCS phase in the left pre-frontal cortex (PreF) and precuneus (PreC). However, only after active tDCS was there significant improvement of pain thresholds measured by quantitative sensory testing, which were correlated with μOR system activation (DosSantos et al., 2014b). Our results suggest that immediate global analgesia induced by the M1-SO tDCS application, sham and active, can be related to the recruitment of endogenous mu-opioid mechanisms.

Analysis: (Aim3) First, we will examine changes in baseline μOR BPND and in the activation of μ-opioid neurotransmission between pre- and post- 10 active daily HD-tDCS treatments. A mixed model of variance, accounting for age and other potentially influencing variables (e.g., plasma levels of estradiol, testosterone) will be employed. Increases in baseline μOR BPND and in the activation of μ-opioid neurotransmission from pre- to post- 10 HD-tDCS sessions in migraine will be expected, with an approximation towards control values. The Spearman nonparametric test will then be used to assess the correlation between the percentage of change pre- and post- 10 M1-tDCS sessions in the thalamus and each region where it was observed, and that of the acute and chronic pain relief.

11.2. SAMPLE SIZE CONSIDERATIONS

Taking into consideration a possible 20% dropout during the study, our sample size of 30 patients per group is a conservative number. For comparing two groups in Aim1 and Aim2, a sample size of 24 in each group will have 80% power to detect an effect size of 1.2 using a two-group t-test with a 0.05 two-sided significance level. For Aim3, baseline vs placebo/active M1 HD-tDCS, a sample size of 24 will have 80% power to detect an effect size of 0.8 using a paired t-test with a 0.05 two-sided significance level, allowing a wide range (0.1 to 1.0) of observable correlations within pairs.

Using the previous study, we approximated the SD as 20%/4 = 5% (range/4), and this gives us a detectable percentage change of 5*0.8=4 or higher.

11.3. PLANNED INTERIM ANALYSES

An interim analysis will be conducted after one year to examine the initial relationships between μOR BP_{ND}, HD-tDCS, and neuropsychological results, and will permit further adjustments. The more complex statistical models for network analysis and HD-tDCS will be powered after the 2nd year. The predictability of effects by the combination of neuropsychological and clinical tests will be used at the end of sample accrual.

11.4. SAFETY REVIEW

A safety review will be conducted if requested by NINDS.

11.5. EFFICACY REVIEW

11.6. FINAL ANALYSIS PLAN

The final analysis plan will be detailed in the Statistical Analysis Plan.

12. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of NINDS and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

13. QUALITY CONTROL AND QUALITY ASSURANCE

Study staff will establish and ensure the quality of processes, data, and documentation associated with clinical research activities. Procedures will encompass both quality control (QC), and quality assurance (QA) activities.

Standard operating procedures (SOPs) and the quality management plan will describe:

- How data will be evaluated for compliance with the protocol and for accuracy in relation to source documents.
- The documents to be reviewed (e.g., CRFs, clinic notes, product accountability records, specimen tracking logs, questionnaires, audio or video recordings), who is responsible, and the frequency for reviews.
- Who will be responsible for addressing quality assurance issues (correcting procedures that are not in compliance with protocol) and quality control issues (correcting errors in data entry).
- Staff training methods and how such training will be tracked.
- Exercises conducted prior to and during the study to train examiners and maintain acceptable intra- and inter-examiner agreement (as applicable).

14. ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1. ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

14.2. INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

14.3. INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

14.4. EXCLUSION OF WOMEN, MINORITIES, AND CHILDREN (SPECIAL POPULATIONS)

We will recruit and study a total of 60 patients diagnosed with episodic migraine, and 20 gender- and age-matched healthy controls, 18-65 years old (inclusive), during the 5-year course of the study. We will use the demographic and PET/MRI data from 10 additional healthy controls, who were recruited and scanned during the NINDS-K23-NS062946 project. Women and men will be recruited at a ratio of 3:1 to reflect the gender ratio prevalence of migraine in our population.

We will recruit without regard to ethnicity, and anticipate that this will reflect the racial characteristics of the general population in this region of the country. According to 2000 census data, the demographic composition of Washtenaw County is 75% White, 12% Black, 5% Asian/Pacific Islanders, 12% Hispanic or Latino (of any race), <1% American Indian/Eskimo/Aleut, and 1% Other.

We are proposing to study subjects between the ages of 18-65. Young children would be unable to participate because of blood volume limits and the utilization of ionizing radiation (PET). We draw up to 120 ml of blood in these studies, which is over the allowable guidelines for younger children. In addition, we utilize daily sessions of HD-tDCS that require careful monitoring of internal states and accurate reporting, which may be difficult to tolerate and perform for children.

14.5. SUBJECT CONFIDENTIALITY

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the funding sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records after the study monitor has signed a University of Michigan confidentiality agreement.

14.6. FUTURE USE OF STORED SPECIMENS

Blood samples may be stored for potential analyses, including genetic investigation, after completion of this study. The informed consent document provides information to subjects regarding the option of participation in this sub-study, as well as their rights as subjects, and the responsibilities of the investigative team with regard to the samples and the related data.

15. DATA HANDLING AND RECORD KEEPING

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

15.1. DATA MANAGEMENT RESPONSIBILITIES

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

15.2. DATA CAPTURE METHODS

Data will be recorded on paper Case Report Forms as well as by electronic systems from which research data will be transferred to study databases.

15.3. TYPES OF DATA

Data will be captured in three primary formats:

- By hand, on paper
- Electronically, on eCRFs
- Electronically, by instruments of the study.

The latter will be transferred to a study database, which will be analyzed by study staff.

15.4. TIMING/REPORTS

The schedule and content of reports will be agreed upon between the PI and NIH-NINDS.

15.5. STUDY RECORDS RETENTION

Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH.

No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

15.6. PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the subject, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

All deviations from the protocol must be addressed in study subject source documents and promptly reported to NINDS and the local IRB, according to their requirements.

15.7. PUBLICATION POLICY

This study will comply with the *NIH Public Access Policy*, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as *ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NINDS grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials:"

Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;

Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

NIH grantees must take specific *steps to ensure compliance* with NIH implementation of FDAAA.

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SUPPLEMENTAL Materials

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modificationså to these documents do not require protocol amendments.

- Statistical Analysis Plan
- Manual of Procedures
- Blood Sampling and Processing Instructions
- Quality Management Plan
- Data Management Plan
- Clinical Monitoring Plan

APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

APPENDIX B: QUESTIONNAIRES

APPENDIX A: SCHEDULE OF EVENTS

Procedures	Phone PreScreening (Day –56 to -22)	Screening (Day -21 to -1)	PET/MRI #1 (Day -21 to -1)	HD-tDCS #1-10 (Days 0-4 & Days 7-11[2])	PET/MRI #2 (Day 16 ± 2)	Follow Up Week #1 (Day 16 ± 2)	Follow Up Month #1 (Day 37 ± 2)	Follow Up Month #2 Day 65 ± 2)	Early Termination[3]
Prescreening Script/Checklist	X								
Informed Consent		X							
Adverse Events		X	X	X	X	X	X	X	X
Medical/Dental History and Physical		X							
Medication History/ Concomitant Medications		X	X	X	X	X	X	X	
Pregnancy Test (Dipstick) and Drug Screen[4]			PET Only		PET Only				
Quantitative Sensory Testing (QST)			X		X				
Eligibility Assessment[5]		X							
RANDOMIZATION		X[6]	X[6]						
PET			X		X				
Sustained Thermal Pain Threshold Stress (STPTS) PET Challenge			X		X				
Blood Sampling[7] • Single Draw, Genetics • Serial Samples, Biomarkers			PET Only		PET Only				
MRI			X		X				
HD-tDCS (M-F for 2 weeks)				10X[8]					

[2] Missed days can be doubled within the (M-F) x 2 schedule and with study team approval

[3] If subject completes an in-person visit

[4] Safety screen for ^{11}C-carfentanil

[5] Schedule subject visits and provide subject with instructions (PET & MRI)

[6] Subjects will be randomized after they have met eligibility and have been consented. This will occur prior to Day 0

[7] If subject has consented to sample future use sub-study.

[8] See Section 6 for active vs healthy volunteer treatment paradigm

Procedures	Phone PreScreening (Day –56 to -22)	Screening (Day -21 to -1)	PET/MRI #1 (Day -21 to -1)	HD-tDCS #1-10 (Days 0-4 & Days 7-11[2])	PET/MRI #2 (Day 16 ± 2)	Follow Up Week #1 (Day 16 ± 2)	Follow Up Month #1 (Day 37 ± 2)	Follow Up Month #2 Day 65 ± 2)	Early Termination[3]
Questionnaires									
Demographics		X[9]							
MIDAS Questionnaire		X[9]							
Beck Depression Inventory		X[9]							
"Expectation of Effect"		X							
McGill Pain Questionnaire (Long Form)		X							
McGill PQ (Short Form)		X	X	X	X	X	X	X	
PANAS[9]		X[9]	X[9]	X	X	X	X	X	
GeoPain (via iPad)[8]		X	X	X	X	X	X	X	
Visual Analog Pain Scale[8]		X	X	X	X	X	X	X	
Allodynia Questionnaire		X	X		X	X	X	X	
PET Subject Information Sheet			X[9]		X				
Pittsburgh Sleep Quality Index		X[9]				X	X	X	
tDCS AE Questionnaire				X	X	X	X	X	
H.O.P.E. Questionnaire						X	X	X	

[9] At Screening, Before and After MRI/PET Scans and tDCS Sessions, and at Follow Up Visits
[9] Questionnaires to be completed by healthy volunteer subjects at the timepoints indicated

APPENDIX B: QUESTIONNAIRES

DEMOGRAPHICS

BECK DEPRESSION INVENTORY

MIDAS QUESTIONNAIRE

VISUAL ANALOG SCALE (VAS) EXPECTATION OF EFFECT

MCGILL PAIN QUESTIONNAIRE (LONG)

MCGILL PAIN QUESTIONNAIRE (SHORT)

PANAS

GEOPAIN™

VISUAL ANALOG SCALE PAIN MEASURE

ALLODYNIA QUESTIONNAIRE

PITTSBURGH SLEEP QUALITY INDEX

tDCS SIDE EFFECTS QUESTIONNAIRE

H.O.P.E. QUESTIONNAIRE

DEMOGRAPHIC QUESTIONNAIRE

Demographic Questions

1. When were you born..... _____/_____/_____?
Month Day Year

2. What is your gender? **(Circle one answer)**

Male..... 1
Female 2

3. Would you describe yourself as . . .? **(Circle one answer)**

Hispanic 1
Not Hispanic 2

Black or African-American 1
White 2
Hispanic or Latino 3
Native American 4
Asian or Pacific Islander 5
Other 6

4. What is your marital status? **(Circle one answer)**

Never married 1
Married 2
Living with someone as if you were married 3
Separated 4
Divorced 5
Widowed 6

5. What is the highest grade or degree in school you completed? ..... _____
(The G.E.D. counts as grade 12)

6. What is your occupation or line of work? If you are unemployed, what was your last job?

_____
OCCUPATION OR LAST JOB

7. Are you currently employed? **(Circle one answer)**

Yes, Full-time 1
Yes, Part-time 2
No 3

8. If unemployed, what is the **main** reason you are not currently employed? **(Circle one answer)**

Student 1
Poor health or disabled 2
Retired 3
Homemaker 4
Laid off 5
Jail 6
Other (please describe in the space below) 7

9. Do you have a valid driver's license? **(Circle one answer)**

Yes 1
No 2

10. Do you have an automobile available for your use? **(Circle one answer)**

Yes 1
No 2

11. Which category **best** describes your living situation at this time?
(Circle one answer)

A house or apartment 1
A rooming house or hotel 2
A halfway house or group home 3
Other 4

Please Describe_____

12. With whom do you live now? **(Circle one answer on each line)**

	YES	NO
Alone	1	2
With spouse or partner	1	2
With children	1	2
With brothers or sisters	1	2
With parents	1	2
With other relatives	1	2
With friends	1	2
With other boarders	1	2
Other	1	2

13. How many children under the age of 16 are currently living with you? ..... _____ children

(If none, enter 0)

14. In the last year, what was your total household income?..... $_____

15. Do you have enough money to take care of your financial needs? **(Circle one answer)**

Definitely yes 1
Mainly yes 2
Mainly no 3
Definitely no..... 4

MIDAS QUESTIONNAIRE

This form can help you and your doctor improve the management of your headaches

Do You Suffer From

headaches?

MIDAS QUESTIONNAIRE

INSTRUCTIONS: Please answer the following questions about ALL your headaches you have had over the last 3 months. Write your answer in the box next to each question. Write zero if you did not do the activity in the last 3 months.

1	On how many days in the last 3 months did you miss work or school because of your headaches?	☐☐	days
2	How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (*Do not include days you counted in question 1 where you missed work or school*)	☐☐	days
3	On how many days in the last 3 months did you not do household work because of your headaches?	☐☐	days
4	How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? (*Do not include days you counted in question 3 where you did not do household work*)	☐☐	days
5	On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?	☐☐	days
	TOTAL	☐☐	days
A	On how many days in the last 3 months did you have a headache? (*If a headache lasted more than 1 day, count each day*)	☐☐	days
B	On a scale of 0–10, on average how painful were these headaches? (*Where 0 = no pain at all, and 10 = pain as bad as it can be*)	☐	

Once you have filled in the questionnaire, add up the total number of days from questions 1–5 (ignore A and B).

Grading system for the MIDAS Questionnaire

Grade	*Definition*	*Score*
I	*Little or no disability*	*0–5*
II	*Mild disability*	*6–10*
III	*Moderate disability*	*11–20*
IV	*Severe disability*	*21+*

MIDAS
MIGRAINE DISABILITY ASSESSMENT PROGRAMME

The MIDAS programme is sponsored by

AstraZeneca

BECK DEPRESSION INVENTORY

BECK DEPRESSION INVENTORY

Please read each group of statements carefully. Then pick out the one statement in each group that best describes the way you have been feeling the PAST WEEK, INCLUDING TODAY. Circle the number besides the statement you picked. If several statements in the group seem to apply equally well, circle each one. Be sure to read all the statements in each group before making your choice.

1. [0] I do not feel sad.
   [1] I feel sad.
   [2] I am sad all of the time and can't snap out of it.
   [3] I am so sad or unhappy that I can't stand it.

2. [0] I am not particularly discouraged about the future.
   [1] I feel discouraged about the future.
   [2] I feel I have nothing to look forward to.
   [3] I feel that the future is hopeless and that things cannot improve.

3. [0] I do not feel like a failure.
   [1] I feel I have failed more than the average person.
   [2] As I look back on my life, all I can see is a lot of failure.
   [3] I feel I am a complete failure as a person.

4. [0] I get as much satisfaction out of things as I used to.
   [1] I don't enjoy things the way I used to
   [2] I don't get real satisfaction out of anything
   [3] I am dissatisfied or bored with everything.

5. [0] I don't feel particularly guilty
   [1] I feel guilty a good part of the time.
   [2] I feel quite guilty most of the time
   [3] I feel guilty all of the time.

6. [0] I don't feel I am being punished.
   [1] I feel I may be punished.
   [2] I expect to be punished.
   [3] I feel I am being punished.

7. [0] I don't feel disappointed in myself.
   [1] I am disappointed in myself.
   [2] I am disgusted with myself.
   [3] I hate myself

8. [0] I don't feel I am any worse than anybody else.
   [1] I am critical of myself for my weaknesses or mistakes.
   [2] I blame myself all the time for my faults.
   [3] I blame myself for everything bad that happens.

9. [0] I don't have any thoughts of killing myself.
   [1] I have thoughts of killing myself but I would not carry them out.
   [2] I would like to kill myself.
   [3] I would kill myself if I had the chance.

10. [0] I don't cry any more than usual.
    [1] I cry more now than I used to.
    [2] I cry all the time now.
    [3] I used to be able to cry but now I can't cry even though I want to.

11. [0] I am no more irritated now than I ever was.
    [1] I get annoyed or irritated more easily than I used to.
    [2] I feel irritated all the time now.
    [3] I don't get irritated at all by the things that used to irritate me.

12. [0] I have not lost interest in other people.
    [1] I am less interested in other people than I used to be.
    [2] I have lost most of my interest in other people.
    [3] I have lost all of my interest in other people.

13. [0] I make decisions about as well as I ever could.
    [1] I put off making decisions more than I used to.
    [2] I have greater difficulty in making decisions than before.
    [3] I can't make decisions at all anymore.

14. [0] I don't feel I look any worse than I used to.
    [1] I am worried that I am looking old or unattractive.
    [2] I feel that there are permanent changes in my appearance that make me look unattractive.
    [3] I believe that I look ugly.

15. [0] I can work about as well as before.
    [1] It takes an extra effort to get started at doing something.
    [2] I have to push myself very hard to do anything.
    [3] I can't do any work at all.

16. [0] I can sleep as well as usual.

[1] I don't sleep as well as I used to.
[2] I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
[3] I wake up several hours earlier than I used to and cannot get back to sleep.

17. [0] I don't get more tired than usual.
[1] I get tired more easily than I used to.
[2] I get tired from doing almost anything.
[3] I am too tired to do anything.

18. [0] My appetite is no worse than usual.
[1] My appetite is not as good as it used to be.
[2] My appetite is much worse now.
[3] I have no appetite at all anymore.

19. [0] I haven't lost much weight, if any, lately.
[1] I have lost more than 5 pounds.
[2] I have lost more than 10 pounds.
[3] I have lost more than 15 pounds.

I am purposefully trying to lose weight by eating less. YES [ ] NO [ ]

20. [0] I am no more worried about my health than usual.
[1] I am worried about physical problems such as aches and pains, upset stomach or constipation.
[2] I am very worried about physical problems and it's hard to think of much else.
[3] I am so worried about my physical problems that I cannot think about anything else.

21. [0] I have not noticed any recent change in my interest in sex.
[1] I am less interested in sex than I used to be.
[2] I am much less interested in sex now.
[3] I have lost interest in sex completely.

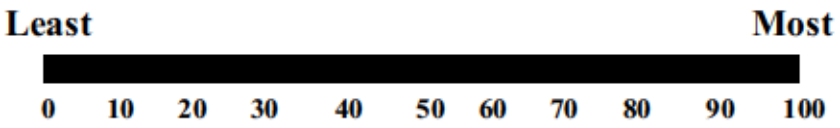
EXPECTATION OF EFFECT

Subject ID : _____

Date: _____

Visual Analog Scale
Expectation of Effect

Please rate how effective you think the therapy will be:
(Circle corresponding number)



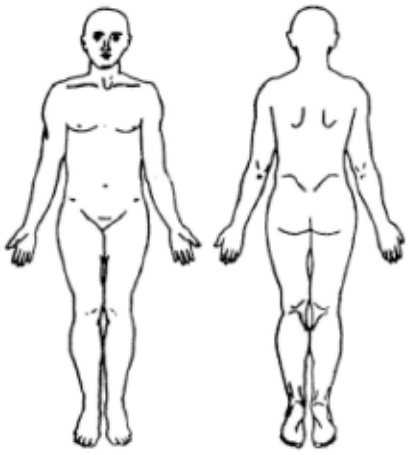
MCGILL PAIN QUESTIONNAIRE (LONG FORM)

McGill Pain Questionnaire

Patient's Name _____ Date _____ Time _____ am/pm

PRI: S _____ (1-10) A _____ (11-15) E _____ (16) M _____ (17-20) PRI(T) _____ (1-20) PPI _____

1 FLICKERING	11 TIRING	BRIEF
QUIVERING	EXHAUSTING	MOMENTARY
PULSING	12 SICKENING	TRANSIENT
THROBBING	SUFFOCATING	RHYTHMIC
BEATING	13 FEARFUL	PERIODIC
POUNDING	FRIGHTFUL	INTERMITTENT
2 JUMPING	TERRIFYING	CONTINUOUS
FLASHING	14 PUNISHING	STEADY
SHOOTING	GRUELLING	CONSTANT
3 PRICKING	CRUEL	
BORING	VICIOUS	
DRILLING	KILLING	
STABBING	15 WRETCHED	
LANCINATING	BLINDING	
4 SHARP	16 ANNOYING	
CUTTING	TROUBLESOME	
LACERATING	MISERABLE	
5 PINCHING	INTENSE	
PRESSING	UNBEARABLE	
GNAWING	17 SPREADING	
CRAMPING	RADIATING	
CRUSHING	PENETRATING	
6 TUGGING	PIERCING	
PULLING	18 TIGHT	
WRENCHING	NUMB	
7 HOT	DRAWING	
BURNING	SQUEEZING	
SCALDING	TEARING	
SEARING	19 COOL	
8 TINGLING	COLD	
ITCHY	FREEZING	
SMARTING	20 NAGGING	
STINGING	NAUSEATING	
9 DULL	AGONIZING	
SORE	DREADFUL	
HURTING	TORTURING	
ACHING		
HEAVY		
10 TENDER	PPI	
TAUT	0 NO PAIN	
RASPING	1 MILD	
SPLITTING	2 DISCOMFORTING	
	3 DISTRESSING	
	4 HORRIBLE	
	5 EXCRUCIATING	



E = EXTERNAL
I = INTERNAL

COMMENTS:

MCGILL PAIN QUESTIONNAIRE (SHORT FORM)

SHORT-FORM McGILL PAIN QUESTIONNAIRE

RONALD MELZACK

PATIENT'S NAME: _____ **DATE:** _____

	NONE	MILD	MODERATE	SEVERE
THROBBING	0) _____	1) _____	2) _____	3) _____
SHOOTING	0) _____	1) _____	2) _____	3) _____
STABBING	0) _____	1) _____	2) _____	3) _____
SHARP	0) _____	1) _____	2) _____	3) _____
CRAMPING	0) _____	1) _____	2) _____	3) _____
GNAWING	0) _____	1) _____	2) _____	3) _____
HOT-BURNING	0) _____	1) _____	2) _____	3) _____
ACHING	0) _____	1) _____	2) _____	3) _____
HEAVY	0) _____	1) _____	2) _____	3) _____
TENDER	0) _____	1) _____	2) _____	3) _____
SPLITTING	0) _____	1) _____	2) _____	3) _____
TIRING-EXHAUSTING	0) _____	1) _____	2) _____	3) _____
SICKENING	0) _____	1) _____	2) _____	3) _____
FEARFUL	0) _____	1) _____	2) _____	3) _____
PUNISHING-CRUEL	0) _____	1) _____	2) _____	3) _____

NO PAIN |——————————————————————| WORST POSSIBLE PAIN

P P I

0	NO PAIN	_____
1	MILD	_____
2	DISCOMFORTING	_____
3	DISTRESSING	_____
4	HORRIBLE	_____
5	EXCRUCIATING	_____

POSITIVE AND NEGATIVE AFFECT SCHEDULE (PANAS-X) QUESTIONNAIRE

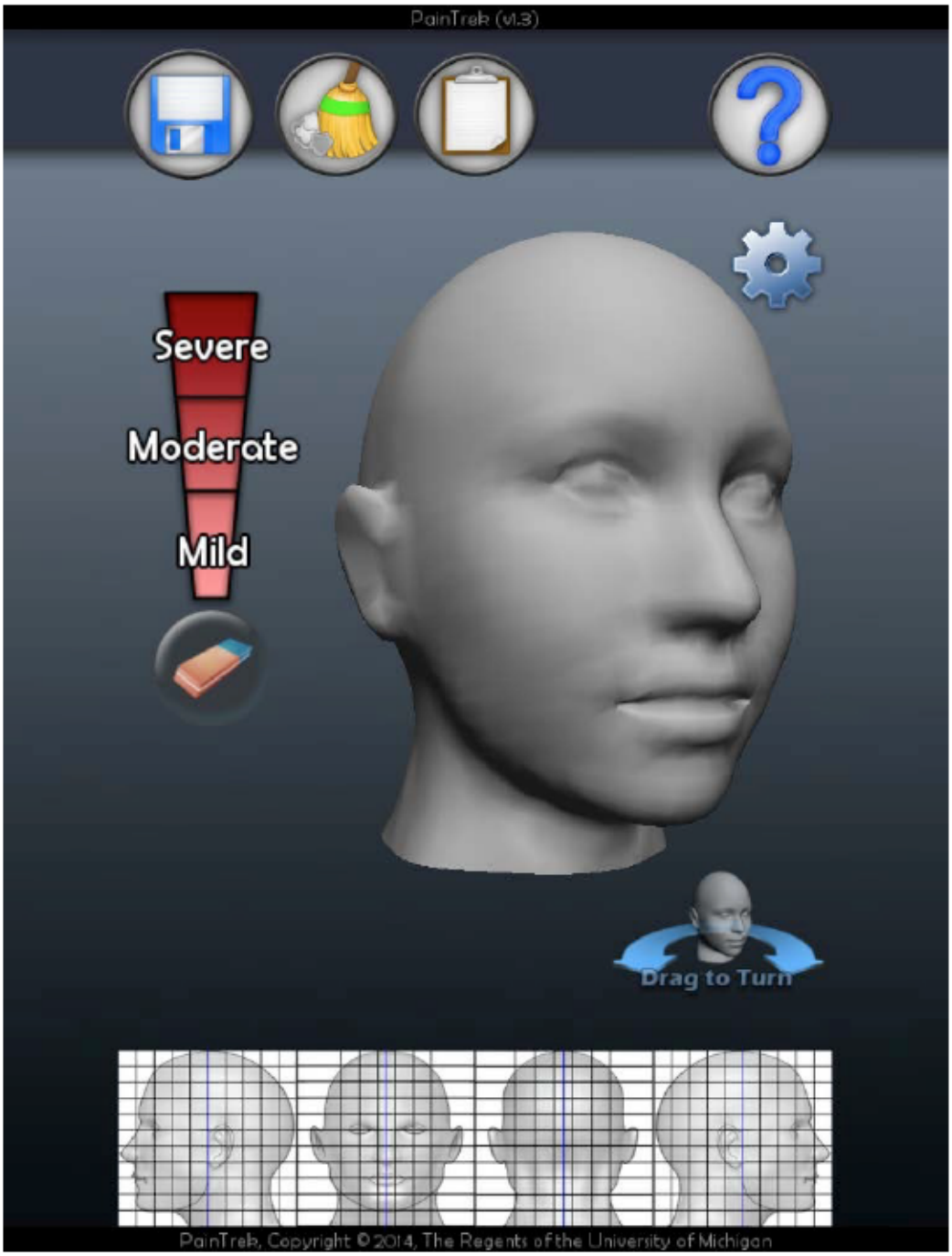
PANAS-X

This scale consists of a number of words and phrases that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you felt this way at this moment. Use the following the record your answers.

1 very slightly or not at all	2 a little	3 moderately	4 quite a bit	5 extremely
____ cheerful	____ sad	____ active		____ angry at self
____ disgusted	____ calm	____ guilty		____ enthusiastic
____ attentive	____ afraid	____ joyful		____ downhearted
____ bashful	____ tired	____ nervous		____ sheepish
____ sluggish	____ amazed	____ lonely		____ distressed
____ daring	____ shaky	____ sleepy		____ blameworthy
____ surprised	____ happy	____ excited		____ determined
____ strong	____ timid	____ hostile		____ frightened
____ scornful	____ alone	____ proud		____ astonished
____ relaxed	____ alert	____ jittery		____ interested
____ irritable	____ upset	____ lively		____ loathing
____ delighted	____ angry	____ ashamed		____ confident
____ inspired	____ bold	____ at ease		____ energetic
____ fearless	____ blue	____ scared		____ concentrating
____ disgusted with self	____ shy	____ drowsy		____ dissatisfied with self

GEOPAIN™

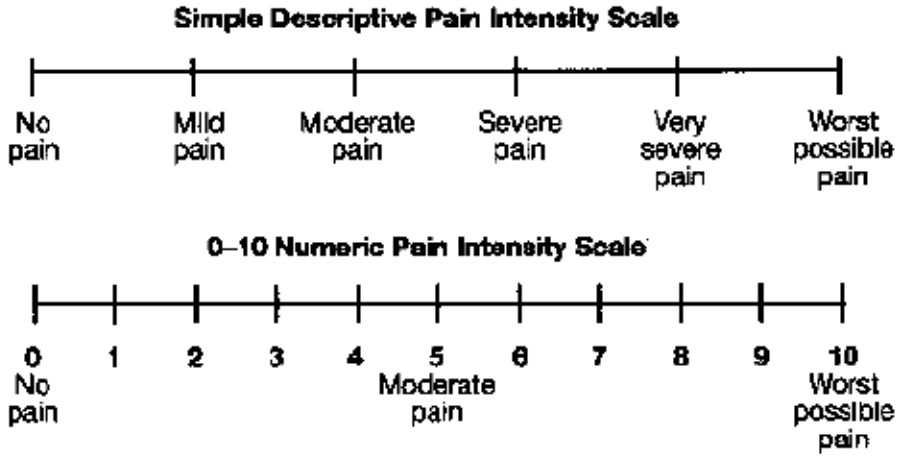
GeoPain™



Disclaimer: Dr. Alexandre DaSilva and Eric Maslowski are the creators of PainTrek (now GeoPain), and also co-founders of MoxyTech, Inc, which licensed the technology from University of Michigan.

VISUAL ANALOG SCALE

Visual Analog Pain Scale



ALLODYNIA QUESTIONNAIRE

The Daily Allodynia Symptom Checklist

Allodynia Diary **Name:**_____

Month:_____

"***Complete this at the end of each day:*** Today I had pain or an unpleasant sensation on my skin while I was":

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Combing my hair																														
Pulling my hair back (e.g., ponytail)																														
Taking a shower (when the water hits my face)																														
Wearing contact lenses																														
Wearing eyeglasses																														
Wearing a necklace																														
Wearing tight clothing																														
Resting my face or head on a pillow																														
Exposed to heat (e.g. cooking, hot water)																														
Exposed to cold (eg ice pack, cold water on face																														
Shaving my face																														
Total score																														

Scoring: 0-Disagree, 1-agree, 2-strongly agree

Allodynia	ASC range
None	(0-2)
Mild	(3-5)
Moderate	(6-8)
Severe	(9 or more)

The 12-item Allodynia Symptom Checklist (ASC-G).

Question: How often do you experience increased pain or an unpleasant sensation on your skin during your most severe type of headache when you engage each of the following?	Does not apply to me	Never	Rarely	Less than half the time	Half the time or more
	Score: 0	Score: 0	Score: 0	Score: 1	Score: 2
Combing your hair					
Pulling your hair back (e.g., ponytail)					
Shaving your face					
Wearing eyeglasses					
Wearing contact lenses					
Wearing earrings					
Wearing a necklace					
Wearing tight clothing					
Taking a shower (when shower water hits your face)					
Resting your face or head on a pillow					
Exposure to heat (e.g. cooking, washing your face with hot water)					
Exposure to cold (e.g. using an ice pack, washing your face with cold water)					
Total score					
Sum of total scores					

Allodynia	ASC range
None	(0-2)
Mild	(3-5)
Moderate	(6-8)
Severe	(9 or more)

PITTSBURGH SLEEP QUALITY INDEX

Subject's Initials_____ ID#_____ Date_____ Time_____ AM PM

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

   BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

   GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Wake up in the middle of the night or early morning

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Have to get up to use the bathroom

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Cannot breathe comfortably

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Cough or snore loudly

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

f) Feel too cold

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

g) Feel too hot

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

h) Had bad dreams

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

i) Have pain

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

j) Other reason(s), please describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

A very big problem _____

10. Do you have a bed partner or room mate?

No bed partner or room mate _____

Partner/room mate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

b) Long pauses between breaths while asleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

c) Legs twitching or jerking while you sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

d) Episodes of disorientation or confusion during sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Other restlessness while you sleep; please describe_____

_____

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

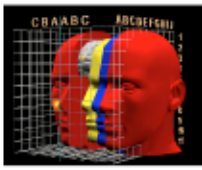
Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: Psychiatry Research, 28:193-213, 1989.

TDCS SIDE EFFECTS

tDCS Side Effects

Do you experience any of the following symptoms or side effects?	*Enter a value (1-4) in the space below.* *1-Absent* *2-Mild* *3-Moderate* *4-Severe*	*If present: Is this related to tDCS?* *1-None* *2-Remote* *3-Possible* *4-Probable* *5-Definite*	*Notes*
Headache			
Neck Pain			
Scalp Pain			
Scalp Burns			
Tingling			
Skin Redness			
Sleepiness			
Trouble Concentrating			
Acute Mood Change			
Other (specify):			

H.O.P.E. QUESTIONNAIRE



H.O.P.E. OROFACIAL PAIN ASSESSMENT FORM ©
University of Michigan, Ann Arbor

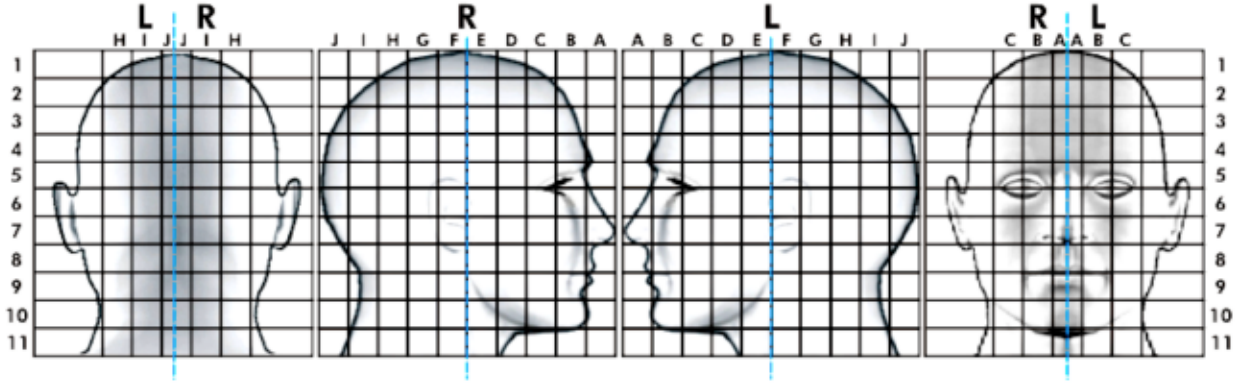
Date: __/__/__ **Sex: M / F**

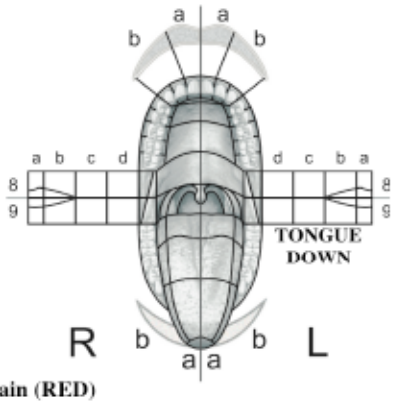
Number: _____ **DOB:** ___/___ **Hand: R / L**
M/Y [1]

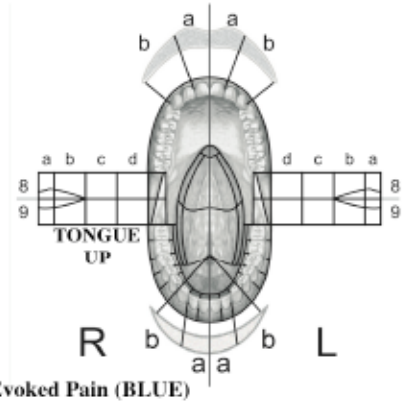
Race:_____

First appointment

Please paint in RED the squares corresponding to the area of your SPONTANEOUS pain, and paint in BLUE the squares corresponding to the area of your EVOKED pain.







Spontaneous Pain (RED)

Please circle the word(s) that best describe(s) the quality of your spontaneous pain.

Throbbing	Gnawing	Splitting
Shooting	Hot-burning	Tiring-exhausting
Stabbing	Aching	Sickening
Sharp	Heavy	Fearful
Cramping	Tender	Punishing-cruel

Please rate the intensity of your average spontaneous pain. Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can imagine

Please rate the unpleasantness of your spontaneous pain. Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10

No unpleasantness — Unpleasant as bad as you can imagine

Evoked Pain (BLUE)

Please circle the word(s) that best describe(s) the quality of your evoked pain.

Throbbing	Gnawing	Splitting
Shooting	Hot-burning	Tiring-exhausting
Stabbing	Aching	Sickening
Sharp	Heavy	Fearful
Cramping	Tender	Punishing-cruel

Please rate the intensity of your evoked pain. Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain as bad as you can imagine

Please rate the unpleasantness of your evoked pain. Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10

No unpleasantness — Unpleasant as bad as you can imagine

How often does your spontaneous pain occur?
Continuously (no headache free time)
Daily - _____ **per day**
Weekly - _____ **per week**
Monthly - _____ **per month**
If not continuous, how long in average does your spontaneous pain last?
__ second(s)
__ minute(s)
__ hour(s)
__days(s)
What does your spontaneous pain better?

Heat	Pregnancy	Particular Position or movement
Cold	Sleep	Medication: _____
Massage	Physical Activity	_____
Isolation		Other: _____

What type of stimuli can aggravate your spontaneous pain?

Menstruation	Brush the hair	Stress
Cold	Neck Movement	Heat
Chewing	Sleepiness	Alcohol
Opening the jaw	Exercise	Light
Noise	food: _____	Other: _____

Please circle the symptoms or signs that you feel or notice during your spontaneous pain.

Nausea	Nasal congestion
Vomiting	Secretion from the nose
Sweating	Dilation of the eye pupil
Sensitivity to noise	Contraction of the eye pupil
Sensitivity to light	Eye redness
Lacrimation	Eyelid edema
Skin redness	Other:_____

Please rate your average activity level during your spontaneous pain. Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10
Leisure High accomplishment
Please rate your average level of social interaction during your spontaneous pain. Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10
Isolation Social gathering
Please rate your average level of attention during your spontaneous pain. Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10
Inattention High awareness
Please rate your average emotional state during your spontaneous pain. Circle the appropriate number below:
- emotions + emotions
sadness/anger,/guilt /fear ↔ happiness/sympathy/gratitude
-10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 +1 +2 +3 +4 +5 +6 +7 +8 +9 +10
Please rate your average level of anxiety during your spontaneous pain. Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10
Least Most
Please rate your average level of nausea during your spontaneous pain. Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10
Least Most

How often does your evoked pain occur?

Daily - _____ **per day**
Weekly - _____ **per week**
Monthly - _____ **per month**
How long in average does your evoked pain last?

__ second(s)
__ minute(s)
__ hour(s)

What does your evoked pain better?

Heat	Pregnancy	Particular Position or movement
Cold	Sleep	Medication: _____
Massage	Physical Activity	_____
Isolation		Other: _____

What type of stimuli can evoke your pain?

Menstruation	Brush the hair	Stress
Cold	Neck Movement	Heat
Chewing	Sleepiness	Alcohol
Opening the jaw	Exercise	Light
Noise	food: _____	Other: _____

Please circle the symptoms or signs that you feel or notice during your evoked pain.

Nausea	Nasal congestion
Vomiting	Secretion from the nose
Sweating	Dilation of the eye pupil
Sensitivity to noise	Contraction of the eye pupil
Sensitivity to light	Eye redness
Lacrimation	Eyelid edema
Skin redness	Other:_____

Please rate your average activity level during your evoked pain. Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10
Leisure High accomplishment
Please rate your average level of social interaction during your evoked pain. Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10
Isolation Social gathering
Please rate your average level of attention during your evoked pain. Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10
Inattention High awareness
Please rate your average emotional state during your evoked pain. Circle the appropriate number below:
- emotions + emotions
sadness/anger,/guilt /fear ↔ happiness/sympathy/gratitude
-10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 +1 +2 +3 +4 +5 +6 +7 +8 +9 +10
Please rate your average level of anxiety during your evoked pain. Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10
Least Most
Please rate your average level of nausea during your evoked pain. Circle the appropriate number below:

0 1 2 3 4 5 6 7 8 9 10
Least Most

What are the therapies, drug and non-drug, which you are currently taking or trying for your pain?

_____
_____
_____
_____

What are the therapies, drug and non-drug, which you have consistently taken or tried before for your pain?

_____
_____
_____
_____

Please list the therapies that you noticed some improvement of your pain.	Circle the percentage of improvement of your "spontaneous pain " (BLUE)	Circle the percentage of improvement of your "evoked pain" (RED)
1)_____ Dosage/frequency: _____ Period taking or using it: _____ Side effects: _____	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain area	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain area
2)_____ Dosage/frequency: _____ Period taking or using it: _____ Side effects: _____	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain area	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain area
3)_____ Dosage/frequency: _____ Period taking or using it: _____ Side effects: _____	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain area	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain area
4)_____ Dosage/frequency: _____ Period taking or using it: _____ Side effects: _____	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain area	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain area
5)_____ Dosage/frequency: _____ Period taking or using it: _____ Side effects: _____	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain area	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain area
6)_____ Dosage/frequency: _____ Period taking: _____ Side effects: _____	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain area	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain area

Please list the therapies that you noticed some improvement of your pain.	Circle the percentage of improvement of your "spontaneous pain " (BLUE)	Circle the percentage of improvement of your "evoked pain" (RED)
7)_____ Dosage/frequency: _____ Period taking or using it: _____ Side effects: _____	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain area	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain area
8)_____ Dosage/frequency: _____ Period taking or using it: _____ Side effects: _____	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain area	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain area
9)_____ Dosage/frequency: _____ Period taking or using it: _____ Side effects: _____	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain area	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain area
10)_____ Dosage/frequency: _____ Period taking or using it: _____ Side effects: _____	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain area	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain area
11)_____ Dosage/frequency: _____ Period taking or using it: _____ Side effects: _____	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain area	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain area
12)_____ Dosage/frequency: _____ Period taking: _____ Side effects: _____	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain area	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain area
13)_____ Dosage/frequency: _____ Period taking: _____ Side effects: _____	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain area	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the evoked pain area
14)_____ Dosage/frequency: _____ Period taking: _____ Side effects: _____	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain area	0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain intensity 0 10 20 30 40 50 60 70 80 90 100% Of improvement in the spontaneous pain area