Understanding the Mechanistic, Neurophysiological, and Antinociceptive Effects of Transcutaneous Auricular Neurostimulation for Treatment of Chronic Pain

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1) Introduction and Purpose

Current management approaches for chronic pain discourage long-term opioid therapy in response to the opioid epidemic and new clinical guidelines (Dowell et al., 2016a). Although opioid prescriptions for pain have declined in recent years, ~8.5 million persons in the U.S. are currently estimated to receive long-term, daily opioid therapy (Guy Jr et al., 2017). Physicians are challenged with the arduous task of transitioning opioid-maintained patients to safer reduced opioid doses, which may result in symptoms of withdrawal such as tachycardia, diaphoresis, nausea and emesis, and anxiety (Darnall et al., 2019; Manhapra et al., 2018). Pharmacological management of these symptoms is limited and can introduce other medications with abuse liability similar to opioids (Kosten & Baxter, 2019).

There is no evidence for a safe nor effective opioid tapering method for chronic pain (Eccleston et al., 2017). A 10-20% reduction in dose every week is recommended by the Centers of Disease Control and Prevention (CDC) for opioid tapering (Dowell et al., 2019; Dowell et al., 2016b) and the Veterans Administration (VA) guidelines for opioid tapering (Sandbrink et al., 2020). An opioid taper decision tool published by the VA describes withdrawal symptoms as non-life-threatening and may not be seen with a gradual taper. Early symptoms such as anxiety/restlessness, runny nose, tearing eyes, sweating and insomnia may be seen in the hours to days after a reduction of opioids. Late symptoms such as tachypnea, yawning, tremor, muscle spasm, nausea, vomiting and diarrhea are seen days to weeks after reduction of dose (Julianne Himstreet, 2016). In this study, we expect that a one-time 10-30% reduction will lead to, at most, slightly elevated pain and mild withdrawal symptoms within 48 hours.

There is limited evidentiary support and mixed success rates for alternative non-pharmacological therapies to reduce opioid use (Mackey et al., 2019). This landscape has given rise to an increasing number of challenging clinical scenarios in which physicians struggle to balance the need to reduce opioid harms with the necessity of maintaining control over pain. There is a great need to expand current treatment options to effective devices that would safely facilitate non-opioid, non-pharmacological pain relief.

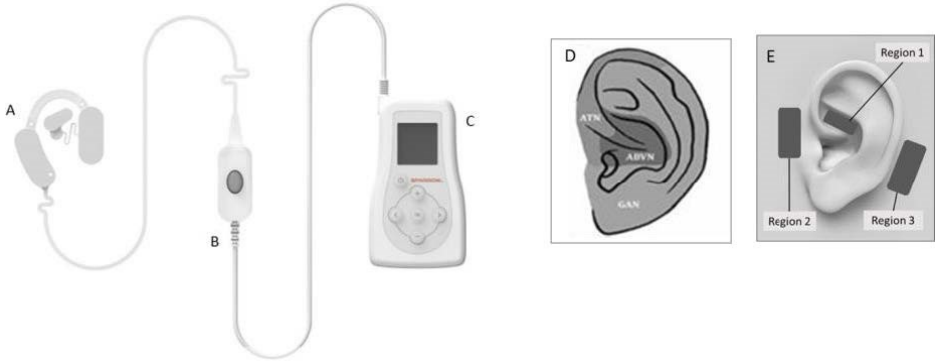
Neuromodulation approaches, such as stimulation of the vagus and trigeminal nerves, have demonstrated antinociception in preclinical and clinical studies (Busch et al., 2013; Farmer et al., 2020; Garcia et al., 2017; Kovacic et al., 2017; Napadow et al., 2012; Straube et al., 2015; Tsang et al., 2011). Stimulation of the auricular branch of the vagal nerve (ABVN) and auriculotemporal trigeminal nerve (ATN), which is a branch of the trigeminal nerve, has been shown to substantially impact opioid withdrawal and pain-related brain activity – ultimately emerging as promising non-pharmacological adjuncts to opioid reduction and therapeutic opioid withdrawal (Badran et al., 2019; Badran, Dowdle, et al., 2018; Badran, Mithoefer, et

al., 2018; Jenkins et al., 2021). Transcutaneous vagus nerve stimulation has been shown to parametrically activate the autonomic nervous system as well as produce reliable direct-brain activation of the vagus afferent network (Badran, Dowdle, et al., 2018). Furthermore, the clinical utility of various forms of neuromodulation have demonstrated reduced need for morphine and fewer withdrawal symptoms in physically dependent neonates and adults (Ellison et al., 1987; FDA, 2021; Jenkins et al., 2021; Miranda & Taca, 2018; Qureshi et al., 2020; Severson et al., 1977; Ward et al., 2020). Recently, Spark Biomedical developed the Sparrow® Therapy System, the first FDA-cleared, wearable non-invasive transcutaneous auricular neurostimulation (tAN) device that targets both the vagus and trigeminal nerve branches via the external ear. Importantly, the clinical data demonstrates analgesia and reduced opioid withdrawal symptoms (FDA, 2021; Jenkins et al., 2021). Evidence suggests that tAN may facilitate this effect by the release of endogenous opioids via activation of afferent subcortical cranial nerve networks, which subsequently modulate higher-order cortical vagal/trigeminal networks mitigating pain. However, rigorous studies are needed to understand tAN mechanisms of action to optimize its clinical efficacy in patients.

2) Background

The Sparrow Ascent Therapy System is a software-controlled, wearable neurostimulation device (**Figure 1**). The Sparrow System is intended to transcutaneously stimulate branches of the vagus and trigeminal nerves on and/or around the ear. The Sparrow Ascent tAN device is based on the Sparrow System 1.0, which received FDA 510(k) clearance (K201873) and is indicated as a transcutaneous nerve field simulator that is intended to be used in patients experiencing opioid withdrawal, however in this paradigm we will be using the device as an anti-pain treatment.

This is the first FDA-cleared device that non-invasively stimulates both the vagus and trigeminal nerves. The Sparrow Ascent System utilizes a flexible earpiece with embedded hydrogel electrodes that adhere to the skin, the earpiece is disposable after use. The system is capable of fully customizing stimulation parameters to match each participants' therapeutic requirements. The stimulation parameters on the device can be set by a physician using a Clinician App (**Figure 1C**). The patient controller device delivers electrical stimulation to the earpiece via a removable cable. Participants can modulate therapy intensity by pressing up/down buttons (**Figure 1B**) and check therapy status with LED lights. The Sparrow Ascent earpiece (**Figure 1A**) is applied for each participant to position the electrodes to stimulate three key dermatome regions (**Figure 1D-E**). These regions are adjacent to several cranial nerves (V, VII, IX, X) and occipital nerves. In particular, the electrodes are located on the cymba concha (**Figure 1E, Region 1**), on the temporomandibular join region, just anterior to the tragus (**Figure 1E, Region 2**), and behind the auricle (**Figure 1E, Region 3**).



Region 1 – ABVN: The subcutaneous tissue in Region 1 is innervated by the auricular branch of the vagus nerve (ABVN), also known as Arnold's nerve (Peuker & Filler, 2002). Arnold's nerve arises from the superior vagal ganglion and is joined by a branch from the inferior ganglion of the glossopharyngeal nerve (Werner et al., 2021).

Region 2 – ATN: The auriculotemporal nerve (ATN) ascends subcutaneously to the electrode located in Region 2. The ATN is a branch of the mandibular division of cranial nerve V (trigeminal nerve). The ATN arises from the mandibular nerve and also communicates with the facial nerve (cranial nerve VII) (Janis et al., 2010; Kwak et al., 2004; Yang & Yoo, 2014).

Region 3 – Mastoid: Branches from the posterior auricular nerve (arising from cranial nerve VII) and branches of the lesser occipital nerve terminate behind the auricle (Netter, 2015). As shown in **Figure 4D-E**, the electrodes in Region 3 are located such that the branches of both the lesser occipital nerve and posterior auricular nerve are subcutaneous to the electrodes.

The Sparrow tAN device 1.0 received 510(k) clearance (K201873) and is indicated as a transcutaneous nerve field stimulator that is intended to be used in patients experiencing opioid withdrawal. The broad FDA-cleared indication for the Sparrow device for patients in opioid withdrawal makes this device an ideal candidate to investigate the mechanisms of action for device-based pain relief in chronic pain patients experiencing pain while tapering off opioid medications in this study.

3) Preliminary Study Results

Drs. Wilkes and Cunningham have completed clinical research on prescription opioid adherence and effective treatment strategies for reducing opioid dependence among chronic pain patients. Recently, this research group completed a Phase I clinical trial testing the feasibility and preliminary effectiveness of a novel medication packaging device that allows for real-time tracking of outpatient prescription opioid use. These results showed that a significant majority of chronic pain patients are non-adherent, thus supporting the need to strategically address novel therapeutics in this at-risk population. In addition, Dr. Wilkes and colleagues have developed novel pain treatment approaches such as pulsed radiofrequency (Nguyen & Wilkes, 2010) and ultra-low-dose intrathecal morphine (Wilkes et al., 2018). Likewise, Dr. Wilkes has extensive clinical experience in prescribing opioids and weaning patients off long-term opioid therapy (Wilkes et al., 2022).

Preclinical and clinical studies have developed tAN clinical practices and stimulation parameters (Badran et al., 2019) and have shown direct brain effects of tAN in healthy adults (Badran, Dowdle, et al., 2018). Likewise, an open-label trial of tAN for neonatal opioid withdrawal syndrome in neonates showed a reduction in opioid withdrawal symptoms when delivered up to four times daily over a maximum of 12 days of treatment, resulting in a reduction in the duration of morphine-aided withdrawal treatment. The tAN treatment was well tolerated and resulted in no unanticipated adverse events (Jenkins et al., 2021).

4) Rationale and Aims

The current project will build on the previous tAN research and clinical studies on chronic pain and opioid withdrawal, ultimately providing a "neural blueprint" of how tAN therapy can mitigate pain and opioid withdrawal symptoms. We will conduct a clinical mechanistic trial of tAN in chronic pain patients tapering from therapeutic opioids. The study will accomplish the following Aim and address the following hypotheses:

Aim: Establish the fMRI neurophysiological signature specifically underlying tAN-based analgesia in chronic pain participants undergoing an opioid taper.

Hypothesis 1: Chronic pain participants who receive tAN stimulation will demonstrate increased fMRI signal activation in vagal afferents within the brainstem compared to sham treatment.

Hypothesis 2: Chronic pain participants who receive tAN will demonstrate decreased fMRI signal activation in the cortical and subcortical pain network compared to sham treatment.

Exploratory Hypothesis 1: tAN-based changes in brain activation will correlate with measures of pain, and the severity of depression and anxiety to specifically delineate the overlay and distinguishing factors between the brain signatures of analgesia, and discomfort.

Inclusion and Exclusion Criteria

The inclusion/exclusion criteria for participants are as follows:

Criteria for Inclusion of Participants:

1. Males and females between 18 and 75 years of age
2. Women of child-bearing age will complete a urine pregnancy test that must be negative. If the test is positive, they will not be enrolled.
3. Participant is able to provide informed consent and function at an intellectual level sufficient for study requirements, as evidenced by an ability to verbally describe the study purpose in their own words.
4. Presence of pain on more than half of the days in the last six months
5. Must have proof of prescribed medication by either showing a prescription bottle with the individual's name or the presence of a prescription on the Prescription Drug Monitoring Program (PDMP)
6. Willingness to taper opioid dose by at least 10%
7. Patient or provider requests opioid dose reduction or discontinuation.
8. Urine Drug Screen (UDS) must be positive for their prescribed opioid
9. Urine Drug Test must be negative for illicit drugs, and nonprescribed opioids
10. Must agree to use nicotine patches and/or gum instead of smoking or vaping in the UTMB facilities

Criteria for Exclusion of Participants:

1. Currently receiving treatment for cancer
2. Participant has a history of epileptic seizures
3. Participant has a history of neurological diseases or traumatic brain injury
4. Participant has abnormal ear anatomy or current ear infection present
5. Participant has presence of devices, e.g., , cochlear prosthesis, neurostimulators
6. Currently receiving a prescription benzodiazepine medication that is not on a regular basis.
7. Currently receiving a dopaminergic medication
8. Current prescription opioid dose <200 MME/day
9. Current abuse of illicit drugs or alcohol (nicotine use is acceptable).
10. Surgery within the previous month
11. Report of suicide attempt or psychiatric hospitalization in the past 5 years.
12. Current suicidal ideation with specific plan or intent
13. Women of childbearing potential must have a negative pregnancy test on day of enrolment.
14. Females who are pregnant or lactating

15. Participant has any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial

5) Recruitment and Consenting Process

Based on *a priori* power analysis in which we estimated the required sample size needed to observe significant effects, we aim to gather a complete dataset from 40 participants (20 males and 20 females, randomly assigned to experimental condition). Our prior experience conducting similar clinical research in pain management has led us to expect a ~33% dropout rate for participants who enter the study. Accordingly, 60 participants will be recruited. These individuals must meet the inclusion/exclusion criteria listed above.

Our study population includes adults who qualify for the study regardless of race/ethnicity or sex. The UTMB Health System is a Medicaid-accepting institution that serves a broad range of patients from various sociodemographic backgrounds in Galveston County. We expect that the sample will be representative of the demographic distribution of the region. Galveston County is 56.7% White (Non-Hispanic), 13.2% Black or African American (Non-Hispanic), 25.4% White (Hispanic), and 6.5% other. For sex, we will enroll an even 50% male and 50% female samples.

We will recruit participants from four sources: UTMB Pain Management Clinics, the UTMB daily announcements, UTMB Epic Slicer Dicer, and from social media. Potential participants are recruited from UTMB Pain Management clinics using flyers placed in waiting rooms and exam rooms, direct clinician referrals, and screening of electronic health records for eligible participants. Patients who are approached for recruitment will be able to decline participation at any time with no change to their healthcare services. Advertisements for the study will be placed in the UTMB Daily Announcement emails, which will provide a phone number for contacting the research team. We will identify participants in the UTMB health system using Epic EMR Slicer Dicer. The pre-screening population will be created with three filters based on study inclusion and exclusion criteria. Criteria include patient status (not deceased), age (18-75), outpatient, and an active prescription for opioid medications in the past 3 months. This search list will be refreshed weekly for the addition of new participants.

Once this list is exported, additional slices may be used to further reduce the list. The study staff will export the Epic medical records and review the remaining chart for inclusion and exclusion criteria. Those meeting criteria will be considered successfully pre-screened. If a successfully pre-screened patient from Slicer Dicer is a clinic patient of Dr. Wilkes (with the established patient-provider relationship), they will be called and introduced to the study using the attached phone script or sent the "Dear Patient letter" via MyChart. If interested, they will be scheduled for the full in-person screening visit.

If the successfully pre-screened patient from Slicer Dicer is a not clinic patient of Dr. Wilkes, one of the following three options will be used.

1.) Dear Patient Letters- Study personnel will provide the treating provider with a list of successfully pre-screened patients and ask permission to contact patient by a recruitment letter ("Dear Patient letter") via MyChart or paper mail to each patient. This letter is attached separately. For MyChart recruitment, with a successful pre-screening, the participants send one MyChart recruitment letter ("Dear Patient letter") and one mailed recruitment letter. If the participant does not respond to this MyChart message or mail, they will not be contacted again.

2.) Dear Doctor Letters - Study personnel will send a letter to the provider ("Dear Doctor letter") asking for the referral of the patients on the pre-screened list. The provider will then give the eligible subjects the study flyer and the investigator's contact information. This flyer is attached separately.
3.) Direct patient contact by calling or an in-clinic approach: Each partnering provider will document in writing that they agree to allow the research team to approach their patients regarding possible participation in research.
    a. For in-person recruitment, study personnel will bring the list of successfully pre-screened patients (from Slicer Dicer) to the provider's clinic. The provider will ask the patient for permission to speak to the research team. If permission is granted, the study personnel will introduce the study and if the patient is interested, schedule for in-person screening visit.
    b. Direct patient calling

Additionally, we will recruit potential participants through a partnership with TrialFacts, who will distribute web advertisements (attached) on social media platforms including Facebook, Instagram, YouTube, Craigslist, Google, as well as their internal email newsletter of persons interested in research participation.

Individuals who respond to TrialFacts ads will be directed to a website landing page (content attached) that provides additional information about the study. If interested, they will complete an online recruitment questionnaire (items attached). Individuals who pass the recruitment questionnaire will then be considered for screening.

Before the screening interview is conducted, all prospective participants will be asked to provide verbal consent to complete screening for study eligibility. We request a waiver of documentation for the screening consent. We will collect formal informed consent if participants pass the screening procedure. During screening, electronic medical records, PDMP, and external electronic records will be reviewed to ensure that participants meet eligibility criteria. Potential participants will be given an overview of the study requirements, risks, and benefits.

During screening, individuals will provide urine for a point-of-care Urine Drug Screen (UDS). If a potential participant lives 50 miles or greater, the UDS will be done at a Quest Diagnostics site of their choosing. Individuals who do not have the necessary results on the UDS will be counseled by study physician, Dr. Wilkes, on the next steps to either reach study eligibility with a repeat test at the UTMB or withdraw from study procedures. The screening data collected will be de-identified and will not be traceable to the prospective participant. Individuals who pass the screening will then be asked to enroll in the study and will be provided with the informed consent document for review.

After passing screening, an admission at the UTMB Clinical Research Center (CRC) will be scheduled.

If they live 50 miles or greater from the CRC, in addition to the subject incentive payment, we will support travel related expenses including mileage, flights, ground transportation, and hotel using standard rates. In the case of extensive travel, we may need to provide lodging for one night before or after the stay. If a meal is needed the night prior to or night after discharge, this will be reimbursed of up to $20 per meal. This will be reimbursed of up to $300 per participant for extended travel.

The study requires an in-patient stay in the UTMB CRC for three nights (approximately 76 hours). Participants will bring their prescribed medication and the medication will be counted by the research staff under the supervision of the participant and a witness. The participant, research staff, and witness

will sign the medication check in form. The medication will be stored in the CRC pixis. We do anticipate study retention issues in a minority of participants who may become bored or irritated during the lengthy in-patient stay. We will provide magazines and a laptop, if desired. In contrast, we do not anticipate high rates of drop out due to adverse events. This rationale is based on several factors. First, persons with chronic pain typically have limited functional activity levels and can be expected to endure a similar experience in tapering from opioids in their home environment. Second, the risk profile of tAN is minimal, and the risks of medically supervised opioid withdrawal are well managed in our study protocol. However, some participants may not enjoy the lack of privacy, unfamiliarity, and standard accommodations associated with in-patient settings (i.e., hospital meals). To accommodate this anticipated issue, we will over-recruit so that 33% could drop out of the study and we would still have enough data to detect significant effects. Up to 60 participants will enroll and initiate the study, and enrollment will cease once 40 participants have completed the study. Study completion will be fostered by the potential benefits associated with continuous medical supervision during opioid withdrawal, potential benefits associated with tAN, and remuneration for participant time and travel. Our research team has experience working with chronic pain participants in clinical trials and recruiting and retaining participants in time-intensive studies. Recruitment of 1-2 participants per month would lead to completion of data collection in 48 months.

6) Source of Research Material

The data to be collected by the research team include screening items, selective review of electronic health record, demographics, quantitative sensory testing, subjective pain severity, opioid withdrawal severity, depression severity, anxiety severity, vital signs, and functional brain activity during magnetic resonance imaging.

Screening items will include questions directly related to inclusion/exclusion criteria and a UDS test. The selective review of the electronic health record will include the following:

- Age
- Gender at birth
- Tobacco use
- Medication history
- Medical diagnoses in previous 12 months
- Vital signs at most recent encounter
- Past doctor visit dates and specialty in previous 12 months
- Results of UDS in the previous 12 months.

A demographics questionnaire (see attached) will include questions related to the following:

- Date of birth
- Sex at birth
- Gender identity
- Ethnicity/Race
- Highest level of education
- Employment status
- Relationship status
- Annual household income
- Disability status
- Pain duration
- Primary Language
- Rural-urban commuting area (RUCA) code

Quantitative sensory testing will involve the following procedures. We will systematically determine information about Aβ (sensory), Aδ (pain), and C (pain tolerance) fiber activity with a 30 × 30 mm thermode attached to a nonpainful (control) site (e.g., form arm) in chronic pain participants (TSA2 thermode; Medoc, Durham, NC, USA). Using the TSA2, we will determine heat sensory, pain, and tolerance thresholds using the method of limits, beginning at 32°C and increasing by 0.5°C per second. Participants will be asked to press a button (to record temperatures) when the stimulus is first detected (sensory threshold), when it becomes painful (pain threshold), and then when the stimulus is intolerable (pain tolerance). When 'intolerable' pain is indicated by the participant, the thermode ceases heating and quickly returns to 32°C within a few seconds. This sensory testing is repeated for five trials to obtain average sensory, pain, and tolerance thresholds. In addition to testing thermal pain thresholds (described above), participants will undergo pressure pain testing using an algometer (Medoc Algomed; Medoc, Durham, NC, USA), a reliable and valid form of pain testing commonly used in neurological research (Kinser et al., 2009). A trained research staff member will press the sensor of the algometer against a painful body region and a non-painful body region (control site), applying increased pressure until the participant reports the sensation as painful (pressure recorded) and intolerable (pressure recorded and testing ceases). The algometer administration will be supervised by another staff member to ensure accurate data recording, and the administrator will remove pressure as soon as participants indicate intolerance. This testing is conducted only once at each time point to avoid pain sensitization.

Structural, functional, and task-based MRI. Participants will undergo a baseline MRI scanning session and the following sequences will be collected:

- *T1 MPRAGE* (10 min). High-resolution structural scans will be obtained using an inversion recovery GeneRalized Autocalibrating Partial Parallel Acquisition (GRAPPA) sequence, 192 slices, voxel size: 1.0 x 1.0 x 1.0 mm, field of view: 256 mm, section thickness:1.0 mm with no gap, giving an in-plane resolution of 256. This sequence will be used for anatomic overlays of the functional data and spatial normalization to a standard atlas, transcranial magnetic stimulation coil positioning, and subsequent voxel-based morphometry. *Field Map* (1 min) Field Map calculations allow for offline correction of imaging distortion during post-processing. Field map configurations will include: flip angle = 60 degrees, field of view = 192 mm; voxel size = 2.0 x 2.0 x 2.0 mm, 72 contiguous slices 2.0 mm thick. In addition, a control fMRI scan of a research staff will be done before enrolling a participant and annually to confirm fMRI setting consistency.

- *Resting-State Functional Connectivity (24 min).* The resting-state scan consists of four 6-minute runs. The first two runs will occur just prior to tAN stimulation (active or sham) and the last two resting-state runs will occur immediately after tAN stimulation (active or sham). All participants will be asked to keep their eyes open and to not fall asleep. Participant's wakefulness during resting-state scans through the use of a) respiratory and heart rate signal and b) eye movement monitoring, in order to ensure participants are not sleeping. *Data processing.* Resting-state functional connectivity will be assessed using the in-house scripts with MATLAB and FSL. First, experimental design variables, pre-processed functional images filtered with a 0.01 to 0.08 Hz band-pass filter, and segmented images will be uploaded into the toolbox. 5-mm radius spheres will be created around a priori regions of interest (such as nucleus accumbens). Individuals' white matter and cerebral spinal fluid templates, heart-rate (HR), respiration rate and movement parameters will be included as covariates. rZ scores for each person will be generated and entered into statistical models.

Neural Pain Tolerance and Reactivity (28 min). The task-based scan will involve delivery of thermal stimuli to the participant's dominant forearm (left or right) using the MRI-compatible TSA2 thermode system (Medoc, Durham, NC, USA). Prior to the first scanning sessions, when participants undergo baseline quantitative sensory testing to assess thermal pain thresholds, we will determine the temperature level at

which the participant reports a pain intensity rating of 7, indicative of moderate pain, on a numerical rating scale (NRS) ranging from 0 to 10 (0 = no pain; 10 = maximum pain tolerable). This temperature level will then be used for delivery of painful thermal stimuli during the evoked fMRI thermal pain paradigm. Once a thermal pain threshold is achieved, innocuous thermal thresholds will be assessed using a descending staircase method. The temperature at which the patient reports the thermal stimulation as no longer painful (a rating of 0/10 on the NRS), but still perceived as warm, will be used for delivery of innocuous thermal stimuli for that individual. For the evoked thermal fMRI paradigm, participants will undergo two functional BOLD runs lasting approximately 14 minutes and consisting of pseudorandomized 8 to 12 second blocks of innocuous (i.e., non-painful) warm temperature stimulation and intermittent noxious (i.e., painful) thermal stimulation set to the level determined during the pain threshold assessment procedure. Stimuli will be separated by intervals (4-8 seconds, rectangular distribution) of baseline temperature (32°C) with a ramp time of 1.6 seconds from baseline to peak temperature (i.e., ramp rate varied based on the target peak temperature). Following each functional BOLD run, participants will be asked to rate their pain intensity using the NRS.

Opioid withdrawal severity will be assessed using several measures. A trained rater will assess severity of opioid withdrawal symptoms using the Clinical Opioid Withdrawal Scale (COWS) (Wesson & Ling, 2003). Likewise, participants will provide their own ratings of withdrawal using the Subjective Opioid Withdrawal Scale (SOWS) (Wesson & Ling, 2003).

Measurement of depression and anxiety will be conducted using several measures. For depression, we will use the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001). For anxiety, the Generalized Anxiety Disorder-7 (GAD-7) (Spitzer et al., 2006). In addition, anxiety resulting from previous stressful or traumatic life events will be assessed using the PTSD Checklist for DSM-5 (PCL-5) (Blevins et al., 2015).

Functional neuroimaging will be conducted at the UTMB Radiology Clinic, located on the UTMB campus in a building adjacent to the Clinical Research Center. A Siemens 3T Skyra scanner equipped with a 32-channel head coil will be utilized for all imaging. Participants will be scanned in resting awake state for 30 minutes. A brief structural scan sequence will be conducted (~10 minutes) along with a functional brain activity scan (~24 minutes) and task-based (thermal evoked pain) scan (~28 minutes). The total amount of time for the complete MRI will be approximately 1 hour and 10 minutes.

For the purposes of participant safety and risk management, participant vital signs (heart rate, body temperature pulse, respiration rate) will be assessed at regular intervals, particularly before and after tAN administration, by a Research Nurse in the UTMB CRC.

7) Randomization, Blinding, and Treatment Administration

All participants will be randomized to one of two stimulation groups (active tAN vs. sham tAN) in a 1:1 fashion such that each group will have 20 participants with complete data. A block randomization procedure will be utilized to ensure that equal numbers of participants are assigned to each of the two conditions.

The programming of either active or sham tAN device will be done by dedicated and unblinded study personnel who will have no additional involvement with participants or data collection. Study personnel will administer active tAN or sham tAN stimulation. No other study staff members at UTMB who interact with participants or collect data will know which type of stimulation the participants received. Participants will additionally remain unaware (e.g., masked) of which type of tAN they are receiving until after study completion.

Active or sham auricular stimulation will be conducted using the FDA-cleared tAN device (Sparrow Ascent®) manufactured by Spark Biomedical (Dallas, TX). The tAN devices are portable, wearable systems with two channels of stimulation (auricular vagus and auricular trigeminal). Two individual

stimulation frequencies will be set: 15 Hz at cymba concha (Region1/Channel 1; vagal innervation) and 100 Hz adjacently anterior to the tragus (Region 2/Channel 2; trigeminal innervation). The pulse duration will be set at 250 μs for all participants. The stimulation intensities (mA) will be set at 1.0 and 1.4 (for Regions 1 and 2, respectively) based on values observed in previous clinical studies. If the participant states that the stimulation intensity is discomforting or imperceivable, the study personnel will gradually decrease/increase the intensity until a comfortable stimulation intensity is achieved. Participants randomized to the sham tAN groups will have the earpiece applied and the cable connected to the Patient Controller, but stimulation will not be administered. The sham device will function, feel, and appear visually identical to an active stimulation device, but will deliver no stimulation. All participants, regardless of condition, will be told that stimulation may or may not be perceived initially and that the Sparrow device will be preparing their neural system for long-term therapy. Participants in both conditions will receive stimulation for a 1-hour training session and at least 4-hours per day for three days (Days 2, 3, and 4). Typically, stimulation will be delivered in four blocks of 1-hour administration, but participants will be allowed to alter this schedule if needed as long as they receive four total hours of tAN per day. Stimulation time will be recorded by study personnel.

When securing the tAN electrodes, the skin will be checked for redness and cleaned daily before placing the left ear electrode. Hydrogel electrodes are placed in front of tragus, and cymba conchae, with a return on the mastoid, securing the wire behind head with hypoallergenic tape, and placing wire under the clothes. The study personnel will verify good electrode contact by monitoring impedance during the session.

STUDY PROTOCOL

Procedures and Flow: Once interested participants are deemed eligible, they will then report to the Clinical Research Center at UTMB, where informed consent will be reviewed and obtained to ensure that the procedures, risks, benefits, and safety protocols are clearly understood. A protocol timeline is described further below.

Screening Interview

- Screening Consent form reviewed
- Data will be collected
  - Conduct interview and review electronic medical records
  - Pregnancy test, if female
  - UDS test
- Participant notified about eligibility
- Informed Consent for full study reviewed and given to participants to review at home prior to reporting to the CRC.
- After having time to review the informed consent document, those still interested in participating will report to the CRC, sign the informed consent document, and begin the study.
- Participants will be given consent, Map, and FAQ to take home

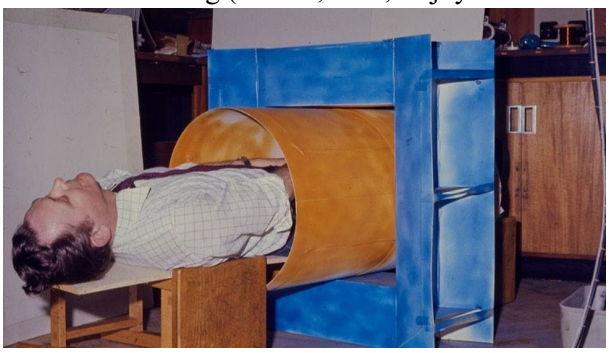
Day 1: Initiate Opioid Taper and Baseline Testing

- Report to CRC at 8:00am
- Sign consent
- UDS and urine pregnancy test obtained

- Randomize into one of the following treatment groups
    - Group 1: Sham tAN
    - Group 2: Active tAN
    - Training session (1 hour)
- Opioid Tapering Protocol. Participants will initiate a one-time 10-30% reduction in opioid dose that will be maintained for the duration of the study. CRC nursing staff will provide participants prescribed opioid medications on set schedules to ensure protocol adherence. Participants will be asked to sign a log indicating when they took each dose of medication. Participants who cannot tolerate or maintain this dose reduction will be allowed to terminate their participation at any time. Although not expected, participants who experience withdrawal symptoms that require adjuvant medications (e.g., clonidine) will be withdrawn from the study.
- Mock MRI Training: In order to mitigate participant's anxiety and/or claustrophobia prior to the MRI session, participants will spend 25-30 minutes in a mock scanner within the CRC (**Figure 2**).

Figure 2. Sample mock (fake) MRI environment.

- Baseline Testing
    - Structural, Functional, and Task-Based Brain Imaging (fMRI)
    - Quantitative Sensory Testing (QST)
    - Subjective Pain Testing (PEG-6; Pain, Enjoyment of Life and General Activity



      Scale)
    - Demographics questionnaire
    - Opioid Withdrawal Severity (COWS/SOWS)
    - Depression and Anxiety Questionnaires (PHQ-9 and GAD-9)
    - Other Questionnaires
        - Patient Reported Outcome Measurement Information System (PROMIS) Physical-Functioning short form 6B
        - PROMIS Sleep disturbance 6A and Sleep duration
        - Pain Catastrophizing
        - Global Satisfaction with Treatment (PGIC)
        - Substance use screener (TAPS1)

Day 2-3: Brain Stimulation

- Neurostimulation. Consistent with the tAN treatment protocol for opioid withdrawal in previous studies (Jenkins et al., 2021), tAN will be administered using the Sparrow device

(active or sham) 4-hours per day for three days (Days 2, 3, and 4). After daily placement of the lead, a picture will record lead placement and will only show the ear and the lead for those who consent. Administration times will typically be broken into four 1-hour administrations, but participants can request alterations to this schedule if needed as long as they receive four total hours of tAN.

- Subjective Pain Assessment. Subjective pain score will be assessed before and after each tAN/sham session using the PEG-6 from 8am to 8pm.
- Opioid Withdrawal Questionnaires. Study personnel will assess severity of opioid withdrawal symptoms using the Clinical Opioid Withdrawal Scale (COWS). Likewise, participants will provide their own ratings of withdrawal using the Subjective Opioid Withdrawal Scale (SOWS) three times a day from 8am to 8pm.

Day 4: Post-Treatment Assessment

- Neurostimulation. 4-hours of stimulation to be administered in the morning (Day 4). Administration times will typically be broken into four 1-hour administrations, but participants can request alterations to this schedule if needed as long as they receive four total hours of tAN.
- QST testing will be done in the same manner as on Day 2. We anticipate observing analgesic effects as demonstrated in a reduction in QST pain and tolerance thresholds, but not necessarily sensory thresholds.
- Subjective Pain score (PEG-6)
- Opioid Withdrawal Questionnaires (COWS/SOWS)
- Depression and Anxiety Questionnaires (PHQ-9, and GAD-9)
- fMRI will be conducted at post-treatment (evening of Day 4).
- Debriefing Plan - Upon conclusion of the study, participants will be asked if they have any further questions or whether any adverse events occurred. They will be instructed to continue the current dose and to schedule a follow up appointment with their provider within two weeks. The stimulation device will be returned to study personnel at the end of the study. The participant's pain physician can contact Spark Biomedical and obtain the stimulation device for participant's continued use at home.

Schedule of Assessments

	Screening for eligibility	1-2 weeks interim	Baseline (Day 1)	tAN administration (Days 2-3)	Post-treatment (Day 4)
Review medical records	X				
UDS test and result	X		X		
Vital signs – blood pressure, heart rate, respiratory rate (every 4h from 8am-8pm on Days 2-3)	X		X	X	X
Urine Pregnancy Test	X		X		
Consent - verbal	X				
Consent - written			X		
Begin Opioid Taper (Reduce daily opioids 10-30%)			X		
Continue reduced daily dose				X	X
MRI			X		X
Thermal Pain Testing			X		X
Pressure Pain Testing			X		X
Neurostimulation (tAN) training			X		
Neurostimulation (tAN)				X	X
Subjective Sensory Testing (pain score) every 4h from 8am – 8pm – PEG-63				X	
COWS/SOWS three times a day from 8am-8pm				X	
Depression questionnaires PHQ-9			X		X
Anxiety questionnaires GAD-7			X		X

PROMIS physical-functioning short form 6b			X		X
PROMIS sleep disturbance 6a and sleep duration			X		X
Pain catastrophizing			X		X
Global satisfaction with treatment			X		X
Substance use screener (TAPS1)			X		X
PTSD check list (PCL-5)			X		X
Brain stimulation experience questionnaire					X
Sham/Active questionnaire					X

8) Adverse Events or Unanticipated Problems

Denise Wilkes, M.D. Ph.D will be charged with the duty of determining the severity rating of adverse events (AE), and with distinguishing serious from non-serious events.

All AEs will be assessed by the clinician using a protocol defined grading system.

- Mild: events require minimal or no treatment and do not interfere with the patient's daily activities.
- Moderate: events result in a low level of inconvenience or concern with the stimulation and/or opioid reduction. Moderate events may cause some interference with functioning.
- Severe: events interrupt a participant's usual activities of daily living and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Life-threatening: any adverse event that places the participant, in the view of the investigator, at immediate risk of death.

Drs. Wilkes and Cunningham will be responsible for monitoring the study and reporting any serious or unanticipated adverse events (SAEs/UPEs) that are considered at least possibly related to the ongoing studies to the IRB, according to IRB standard procedures.

The study staff (PIs, Co-Is, postdoctoral fellows, and clinical research coordinators) are responsible for collecting and recording all clinical data. As these results are collected, all protocol deviations and adverse events will be identified and reported to PIs, graded for severity, and assigned causality, reported to the required entities, and compiled for periodic review at monthly PI and DSMB meetings. After assigning causality, the PIs will decide the course of action for the study participant. The PIs will evaluate every adverse event and determine whether it affects the risk/benefit ratio of the study and whether modifications to the protocol or informed consent are required. An annual report summarizing all AEs will be prepared and reported to the IRB and NIH. Reports of adverse events, protocol deviations, and any other relevant safety information (dropouts, device malfunctions, etc.) will be reviewed by the research team on an ongoing weekly basis at regular meetings, and the research team will discuss whether the study/studies should continue as planned, or if changes are needed, or if the study/studies should be stopped. All AEs in the study time-period will be reported to the IRB and the NIH, with SAEs being reported within 48 hours.

Follow-up plans for SAEs and unresolved unanticipated problems: The Investigators are experienced in following up on subjects with SAEs/UPEs in challenge studies and clinical trials. In general, any subjects experiencing such problems will be followed closely by the investigators and evaluated in person (if necessary) by the investigators or other qualified medical personnel under guidance from the investigators. The subject would be evaluated and re-evaluated as many times as is necessary to ensure safety and the best outcome. Decisions will be made about whether the participant should continue in the study and whether or not any additional referrals are necessary to help with their symptoms. If participants are having ongoing unresolved problems, we will also decide whether or not it is safe for the subject to continue in the study and whether or not additional referrals or assessment or care are necessary. We will work in conjunction with the DSMB, IRB, and NIH on these decisions.

There is an additional potential for incidental findings to occur during functional neuroimaging. For example, if a participant were to have a brain tumor that was previously undiscovered, we may observe this upon viewing scanning data. After fMRI scanning at UTMB, a radiological technician will perform a

cursory review of the scan, and any incidental finding would be communicated immediately to the PI (Dr. Wilkes). All study procedures with that participant would cease until the PI has determined that it is safe for that participant to continue in the study, which may require the participant to see another medical provider and be cleared for participation. If it was determined that the patient needs immediate medical care, they will be withdrawn from the study. If an incidental finding were to be missed by our UTMB radiology team and noticed during analysis of neuroimaging results, the findings will be within 24 hours to the participant.

Potential Risks

Risks of tAN: tAN is a form of cranial nerve stimulation that non-invasively stimulates the auricular branches of the vagus and trigeminal nerves that innervate the ear. This novel therapeutic modality received FDA clearance (K201873) after demonstrating a favorable risk benefit profile in a clinical trial with 26 adult participants with opioid use disorder (study in process). The device has also been safely used in adults, neonates and infants (Jenkins et al., 2021). No device-related adverse events are anticipated with the use of the Sparrow tAN device. Furthermore, no serious adverse events are anticipated from the study procedures, which are performed routinely in examination of participants with opioid withdrawal. Examples of potential adverse events include:

- Dermal (skin) irritation
- Erythema (redness where device is touching the skin)
- Paresthesia (tingling, prickling or numbness)
- Allergic contact dermatitis (red, itchy rash due to allergy)
- Transient (temporary) pain or discomfort due to stimulation
- Transient pain or discomfort due to device malfunction
- Otalgia/otodynia (earache)
- Muscle twitching during stimulation
- Failure of a device component resulting in loss or decrease of therapeutic effect

Theoretical risks associated with neuromodulation of the parasympathetic nervous system via tAN would also be applicable, including reduction of heart rate, but this has not been reported in the clinical trial in neonates and infants (Jenkins et al., 2021).

The following steps have been taken to minimize the risks associated with the tAN and stimulation discomfort in opioid use disorder patients:

- Hydrogel electrode contacts have demonstrated improved current distribution and minimize skin irritation/discomfort.
- Clearly defined inclusion and exclusion criteria that ensure only appropriate participants are enrolled.
- The tAN device programming and participant training will be performed by healthcare providers or research personnel trained in using the Sparrow Device.
- Participants will be closely followed as part of their treatment and any adverse events (types and rates) will be closely monitored.

The tAN device used in these studies a second-generation system (Sparrow Ascent), which is based on an FDA 510(k) cleared electrical stimulator that meets the rigorous risk management (ISO 14971) and electrical safety standards (IEC 60601-1) of the FDA. In previous clinical studies, Spark Biomedical and others with similar auricular technology have received IRB approvals under non-significant risk (NSR) designation. Given the minimal risk of this already FDA-cleared method, we expect tAN will be a very safe procedure.

Risks of MRI: MRIs are safe and minimal risk procedures in adults. There are currently no known risks of exposure to the MRI environment. One known risk, related to MRI, is that strong magnetic fields attract iron or steel metal objects, leading to safety risks, which are minimized by SOPs among which one of the exclusion criteria of this study: any subject with metallic implants making it unsafe to enter the MRI environment cannot be enrolled. There is also a small risk of discomfort linked to exposure to the noise of the magnet and confined environment which might lead, in some people, to feeling of claustrophobia.

Risks of Loss of Confidentiality: We will assign study numbers to each participant, keep clinical research forms and consent forms in locked offices. Database files will be stored in locked filing cabinets in a secured research office, and upon digitization into an electronic database the data will be kept in an encrypted file on a password-protected computer. All other data files related to this study will be identified by participant number only, without link to standard identifiers. We will publish the aggregate data only. MRI files will be stored by participant study number and date of scan.

Risks of Opioid Tapering: Opioid tapering is often uncomfortable for patients but generally safe. Most patients who are on long-term opioids have experienced opioid withdrawals multiple times due to an interruption/delayed prescription refill. Potential symptoms include: tachycardia, GI upset (stomach cramps, nausea, vomiting, diarrhea), sweating, tremor, restlessness, yawning, mydriasis, anxiety/irritability, bone/joint aches, piloerection (goosebumps), and rhinorrhea or nasal congestion. In rare cases, tachycardia can lead to arrhythmias or myocardial infarction. We will monitor blood pressure and heart rate every 4 hours during the daytime (8am-8pm), in order to not disrupt sleep, in the CRC.

The maximum opioid dose at the start of the study (prior to tapering) is set at 200 morphine milligram equivalents (MME) per day. This limit is consistent with CDC recommendations for maximum daily prescribed opioid dosage (Dowell et al., 2019). Our clinical trial protocol is consistent with expert recommendations for opioid tapering protocols (Dowell et al., 2016b) suggesting that 10-20% dose reduction per week are slow enough to avoid major withdrawal and pain exacerbation.

Forced opioid tapers are generally discouraged outside of extreme circumstances. Therefore, even if tapering is recommended by their provider, participants who enroll in the study must express willingness and desire to reduce their dosage by at least 10% even if they do not want to participate in this study.

Research nurses will continuously monitor patient status and vital signs during the in-patient study period. Should a participant experience intolerable symptoms associated with opioid tapering (or any other adverse events [AEs]), the PI, Dr. Wilkes, will be contacted and determine whether it is safe for the participant to continue participation. Should a participant experience psychological distress (or other similar AEs), the study physician, Dr. Wilkes,, will be contacted to determine whether it is safe for the participant to continue participation. The CRC at UTMB has continuous access to on-call physicians, emergency resuscitation, and rapid admission of participants to the emergency department if a medical emergency occurs. If a participant should require a “rescue dose” of opioids above the maximum tapering dose to mitigate withdrawal symptoms or pain, which is not expected, the participant will be allowed to exceed the taper (by ingesting their taper dosage) and subsequently withdraw from the study.

Participants will additionally be provided with contact information for emergency medical care, counseled on the dangers of using illicit opioids as alternatives for pain relief, and encouraged to contact the study team should any AE occur after study completion. Participants will be instructed to schedule a follow-up visit with their Pain Management provider in 2-weeks.

Study Withdrawal and Discontinuation

Any participant may withdraw from the study by stating so at any time during their participation. Participants will be compensated for the time spent in the CRC, regardless of completion.

The reasons for discontinuation:

- Score on the Clinical Opioid Withdrawal Scale ≥ 36
- Intolerable withdrawal symptoms (such as agitation, insomnia, or vomiting)
- Blood pressure elevated to 180/100 mm/Hg or higher
- Tachycardia (>100 resting bpm) that fails to remit after 30 minutes
- Self-reported onset of suicidal ideation
- Significant verbal or physical aggression toward study personnel, research nurses, or self.

If any of these unlikely events were to occur, the PI, Dr. Wilkes, will be notified. Participant will be given medical care to resolve symptoms, potentially including a rescue dose of opioid medication. Participants will be observed for an hour before sending home. If, in the rare case, symptoms do not resolve, we will encourage participant to be admitted to UTMB for further care.

9) Procedures to Maintain Confidentiality

We will assign study numbers to each participant, keep clinical research forms and consent forms in locked offices. Database files will be stored in locked filing cabinets in a secured research office, and upon digitization into an electronic database the data will be kept in an encrypted file on a password-protected computer. All other data files related to this study will be identified by participant number only, without link to standard identifiers. We will publish the aggregate data only. MRI files will be stored by participant study number and date of scan.

10) Data Safety Monitoring Board

Data used for safety monitoring will include serious adverse events, dropout rates and reasons for dropout, enrollment numbers, subject interviews, protocol compliance, review of symptoms or performance status, review of vital signs, review of evaluation performed, protocol deviations, and blinded data. If it has been determined, for any reason, that there will be a suspension of this study, the PIs will suspend enrollment of new participants but continue intervention/monitoring of previously enrolled participants if it is in the best interest of those participants. We have determined that this study involves greater than minimal risk to participants, but that potential benefits outweigh potential risks.

The Bi-Annual Report will include the following: a summary of all adverse events, confirmation of adherence to the DSMP, a summary of any data and safety monitoring issues since prior reporting period, a description of the changes in the research protocol or DSMP and all new and continuing IRB approvals. Prior to the bi-annual meeting of the DSMB, our study biostatistician, Dr. Yong-Fang Kuo, will review the data and present preliminary results in a report to the DSMB.

The DSMB will consist of the following members:

- F. Gerald Moeller, MD, Virginia Commonwealth University
- Joy Schmitz, PhD, UT Health McGovern Medical School
- Alejandro Villasante-Tezanos, Ph.D., University of Texas Medical Branch

11) Potential Benefits

There are potential benefits associated with continuous medical supervision during opioid withdrawal, such as reduced risk for adverse events and continuous support. Additionally, there are potential benefits associated with tAN, such as reduced pain and opioid withdrawal symptoms as a result of active stimulation.

12) Compensation

Total participant time will require 76 hours of continuous in-patient stay at the Clinical Research Center at UTMB. Based on the time required, burden of assessments, and inconvenience incurred by participants, compensation is calculated at $25 per hour (76 hours x $25 per hour = $1,900 per participant). In addition, travel incidentals will be reimbursed with an additional $100, resulting in total compensation of $2,000 per participant. Participants who live greater than 50 miles from Galveston may receive travel funds up to $300. Participants who live within 50 miles, who need transportation may receive a lyft ride to and from the CRC or a screening appointment. Participants who dropout early will receive pro-rated compensation. We estimate that participants will be recruited at a rate of one to two per month over five years.

13) Statistical Considerations

Sample Size Power Analysis and Biostatistics

Few similar studies have been completed with similar methods (i.e., clinical pain population, cranial nerve stimulation, resting-state fMRI neuroimaging) from which derive an expected effect size. However, a previous study that assessed electroencephalogram potentials in participants who received auricular vagal nerve stimulation vs. sham for migraine found a large effect size for the time X treatment interaction ($f = 1.22$) (Straube et al., 2015), and a study of auricular vagal nerve stimulation in migraine also showed large effect size ($f = 0.73$) related to increased activity in the trigeminal nerve (Garcia et al., 2017). Therefore, with our proposed sample size of 40 and at least medium effect size ($f = 0.25$, $\alpha = 0.05$), the study is sufficiently powered to detect significant main effects and interactions ($1 - \beta = 0.84$).

Interim Analysis

No formal interim analyses will be performed. The purpose of our analysis at the halfway of data collection is to ensure all data is being collected and recorded in a manner that is usable, consistent with our original grant proposal's goals, and will be ready for the final analysis.

We are not going to analyze the effects of the group allocation or submit any of this data for journal publication. Our remaining data collection study procedures will not be affected by our interim analysis findings.

Participant Demographic Characteristics: For the first 20 participants who have completed the study, we will export descriptive data from the RedCap database, clean this in Excel, and our biostatistician will provide the descriptive statistics.

Primary Outcome Measures: For the 20 participants who have completed the study, we will send the fMRI data for each participant to our mUSC collaborator, Xiaolong Peng, and receive back the numerical values for the BOLD signals. We will then submit these values to our biostatistician to ensure they are appropriate for analysis.

Secondary Outcome Measures: For the 20 participants who have completed the study, we will export the quantitative sensory data from the Medoc testing device application, add this to the RedCap database, clean this in Excel, and confirm it is in the proper format for statistical analysis.

14) Data Sharing

A consortium agreement has been established between UTMB, MUSC, and Spark Biomedical, as part of the NIH grant funding this study.

After participants complete the study, demographic and questionnaire data will be analyzed by Dr. Kuo. After a participant completes neuroimaging, the raw imaging data will be stored in a de-identified compressed folder that will be uploaded to OneDrive by study personnel. Raw imaging data will additionally be stored in a secure electronic repository at UTMB. Imaging data will be shared in a HIPPA-compliant fashion using a cloud-based procedure in OneDrive (Microsoft Sharepoint). Imaging analysis will be done at the Center for Biomedical Imaging at the Medical University of South Carolina under the supervision of Dr. Xiaolong Peng.

We will register this study with the NIH HEAL data sharing platform and provide annual updates in accordance with any release of study data as specified by the HEAL data sharing policy.

15) Rigor and Reproducibility

The proposed study will achieve robust and unbiased results via explicit inclusion/exclusion criteria; randomization of treatment condition order and examination of order effects; sham control; double blinding; sophisticated compliance monitoring at UTMB; use of validated MRI, laboratory, and interview/self-report measures; explicit hypotheses; power estimates; planned handling of attrition and missing data; and careful consideration of potential confounds. Methodology is reported in a detailed and fully transparent manner to support replication.

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