PROTOCOL TITLE:
Low Intensity Focused Ultrasound Pulses (LIFUP) to Modulate Pain

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1.0 Objectives/Specific Aims

(Overall background of this technology and this proposal at MUSC now: LIFUP is an interesting new form of brain stimulation that promises to be the 'holy grail' of brain stimulation.(1-3) That is, it may be possible to stimulate non-invasively, safely, deep in the brain with focal precision. If true then we would have a new technology with enormous research and clinical potential. Currently transcranial magnetic stimulation (TMS), which is FDA approved for treating depression and OCD, can only stimulate the surface of the brain and can only stimulate deeper by increasing the intensity, and spreading the field. It is thus not deep and focal but deep and broad. In contrast, deep brain stimulation (DBS), which is FDA approved for treating Parkinson's Disease, can stimulate deep in the brain and quite focally. However, it is invasive and requires brain surgery and an implanted wire. There are surgical risks as well.

The LIFUP device was initially tested in animal models and was shown safe. The FDA then required testing in epilepsy patients who were going to have resection. The group at UCLA did this and examined the tissue for any short-term damage caused by the ultrasound. There was none. Thus, the FDA now treats LIFUP like diagnostic ultrasound and the UCLA IRB has approved several studies in healthy adults and other diseases. The UCLA data in healthy adults (thalamus) were presented last week and are attached in a poster.

The BSL at MUSC is a world leader in brain stimulation and we are excited about this technology. With the approval of IRB II we were the first in the world to perform TMS in the MRI scanner. We hope to become a world leader with this new technology. As our first test, we have chosen to use a pain paradigm within the MRI scanner. Dr. Jeff Borckardt perfected this method years ago and we have used it now in many studies. We will deliver the LIFUP to the thalamus and test whether the thalamus is involved with pain processing and whether LIFUP can alter that. We are experienced at doing pain studies in the scanner. We will get valuable experience with LIFUP with this study and then will likely use it in later studies in depression, anxiety, craving and addiction, etc.

When I first proposed to do TMS in the scanner over 20 years ago the MUSC IRB required that I be the first test subject, and report back. I did that and am prepared to do that here if that is what is needed. I think this LIFUP is as safe as diagnostic ultrasound, and has enormous research and clinical potential.)

Specific Aims.

Aim 1. Test the safety and feasibility of LIFUP to thalamus in healthy volunteers.

Aim 2. Characterize the time course and magnitude of thalamic LIFUP-induced analgesia.

Aim 3. Identify the brain circuitry (BOLD activity) that thalamic LIFUP changes during induced pain.

Hypothesis.

The anterior nuclei of the thalamus in addition to periaqueductal gray (PAG) and rostral ventromedial medulla (RVM) are integral regions of a supraspinal opioidergic structure that regulate pain perception (4-8). With the capability to influence deep neurological tissues, low intensity frequency ultrasound pulsation can likely modulate this circuit and induce analgesia. LIFUP deep brain modulation is achieved by induction of focused mechanical waveforms that traverse the cranium and underlying brain tissue (19). The low frequency of the ultrasonic wave consequently alters neuronal transmission and causes action potential variations through mechanical means, rather than thermal (20). The purpose of this study is to examine whether stimulation of the anterior nuclei of the thalamus via LIFUP induces analgesia. **We hypothesize that suppression of the anterior nuclei of the thalamus will induce a temporary increase**

in pain tolerance. Moreover, the behavioral changes in pain will correlate with specific regional BOLD changes during pain.

3.0 Intervention to be studied – Low intensity Focused Ultrasound Pulses (LIFUP)

(Note, although we will be using MRI scanning and thermal pain assessments, those are established techniques with low risk. The MUSC IRB is quite familiar with those. I will thus concentrate on LIFUP.)

LIFUP uses a single large concave, or multiple ultrasound transducers in a cap placed on the scalp to produce high frequency (100Hz) sonications for 30 seconds at a time for 10 trains of pulses. Unlike traditional diagnostic ultrasound, which constantly transmits ultrasound and 'listens' to the echo to form an image, LIFUP delivers the ultrasound in packets or pulses. For reasons that are not clear, pulsed ultrasound causes neurons to depolarize and fire. Bones typically block ultrasound waves. Cleverly, however, one can deliver the ultrasound from multiple sources and use the skull as a lens, to actually shape and focus the convergent beam deeper in the brain.

The clinical use of LIFUP thus uses MRI scans taken before stimulation to position and calculate how multiple ultrasonic pulsations will converge at a location in the brain (taking into account the bone dispersion of the beam from the skull). Since a small transducer like in diagnostic ultrasound cannot individually cause neuronal discharge, with LIFUP neuronal firing can be focused both deep (2-12cm under the cap; for comparison, traditional TMS can stimulate 1-3.4cm^2 deep(9, 10)) and focally (as small as 0.5mm in diameter, and up to 1000mm; the facility of a standard, commercially-available 70mm figure-of-8 TMS coil is roughly 50$mm^{2; (9, 10)}$). Interestingly, the pulse width of the carrying frequency of LIFUP (0.5ms) is strikingly similar to that used in all other pulsed neuromodulation therapies (DBS: 0.6ms, ECT: 0.5ms; TMS: 0.2ms; VNS: 0.5ms), suggesting that this timeframe is mechanistically meaningful. This is a good example of the common background science of brain stimulation that transcends the individual methods.

Researchers have examined the effects of LIFUP in preclinical and clinical settings, confirming its ability to safely stimulate neural tissue(11-14), proposing cellular mechanisms for its efficacy(13-19), and now using LIFUP in human patients(20). Monti et al. (2016) described a case study in which they used LIFUP to stimulate a comatose patient's thalamus.(20). Two pre-LIFUP assessments rated the patient as being in minimally conscious state (MCS). After sonication, the patient recovered motor and oromotor functions the next day, advancing to full language comprehension and communication by nodding and shaking his head. Five days post-LIFUP, the patient attempted to walk. While this study was neither blinded nor sham-controlled, the first application of therapeutic LIFUP in a human patient was encouraging and we expect more therapeutic applications of LIFUP and potential clinical trials in the future. If LIFUP continues to show clinical potential, it has the potential to supplant the role of DBS without the need for surgery. The key barrier to LIFUP replacing DBS for clinical applications is that by and large, DBS is used in a manner where the device is inserted and turned constantly on without attempting to fundamentally change circuit dynamics or behavior so that you could remove the device. Obviously, patients cannot permanently wear a LIFUP helmet. However, to the degree that we learn how to stimulate in ways that permanently change circuit behavior (LTD or LTP) without ablation, we may be able to substitute several sessions of LIFUP that can train and rewire the brain instead of permanently implanting hardware. LIFUP can certainly stimulate deep and focal and noninvasively and thus may be a key next step in the field of brain stimulation.

Information on the intervention to be studied.

We will be using the Brainsonix Low intensity focused ultrasound pulsation device. (BX Pulsar 1001). Please see the manufacturers description (Technical Summary) along with appendixes about the actual safety of the device itself.

FDA Status of the BX Pulsar 1001 device.

The BX Pulsar device was initially tested at UCLA in epilepsy patients. This research required an FDA IDE, which I have attached to the IRB application. After this study was done and safety was established, the UCLA IRB now does not require an IDE and treats this form of ultrasound just like it does regular diagnostic ultrasound, which is non-significant risk. The diagnostic ultrasound devices and this one are the same in terms of what they can produce. I have attached the letters of approval from the UCLA for using this device in testing memory, Alzheimer's disease, coma, the amygdala and emotions, and the thalamus with healthy controls. I have also attached a list of FDA cleared devices.

Importantly, this device can only deliver the power of a diagnostic ultrasound device. It is not able to deliver the power needed for High Intensity Ultrasound Ablation such as is used in neurosurgery. This would require multiple machines, precisely focused, delivering over 1000 times more energy than we are using.

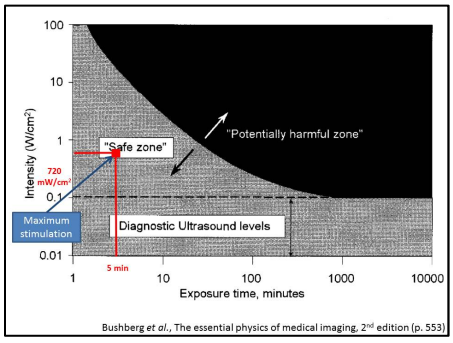
The PI wearing the device (puck) (not connected to the source) demonstrating the position used to reach the thalamus.

For device trials, describe the proposed use of the device as well as its safety.

We will use the device in its intended fashion. We will initially obtain a structural scan of the subjects head. We will then place the ultrasound transducer (sometimes called a puck, as it looks like a hockey puck), on the subjects head using anatomical landmarks as well as Brainsight which we know generally position the device in the correct orientation. We will then take an MRI scan of the brain. The gel that we use between the puck and the skull is able to be seen easily on the scout MRI scan. We can then use MRI guided measurements to adjust the puck in order to position it to be able to stimulate the thalamus. This approach has been used by the UCLA group in their initial epilepsy and now healthy control and other disease studies.

We will then activate the MRI scanner and thermal pain system and then apply LIFUP or not and measure whether there are changes in pain threshold during LIFUP.

With respect to safety, the device is manufactured to certain safety parameters and will not fail or overheat or leak noise. After the initial studies in epilepsy patients, on top of the extensive animal studies, the FDA has now allowed the device to be sold and distributed. The UCLA IRB now realizes that the device is as safe as diagnostic ultrasound.



One way of conceptualizing the issue of safety of LIFUP is as follows.

1) Diagnostic ultrasound is deemed safe, with only minimal limits and concerns.

2) Diagnostic ultrasound is sometimes used almost continuously for 30 minutes to an hour.

3) LIFUP is not able to deliver intensities much greater than diagnostic ultrasound.

4) The amount of time LIFUP is delivered (30 sec) is much less than diagnostic ultrasound.

5) Thus the amount of energy delivered is much less than diagnostic ultrasound.

6) High Intensity Ablative Ultrasound delivers energy that is 100 times greater than LIFUP.

Why it is important to develop a non-opiate method of treating pain. Though safe and successful in most clinical settings, opioid anesthetics are limited by dose-dependent side effects and potential abuse (21). Past data indicate that risk of fatal opiate overdose is directly related to maximum prescribed daily dose (22). Moreover, studies of opiate abuse have shown that emergency room visits and fatal poisonings caused by nonmedical use of opioid analgesics have more than doubled and tripled, respectively, within the last decade (23, 24). These morbidity and mortality data demonstrate an urgent need to discover adjunctive therapies for pain management.

Brain stimulation methods are a promising avenue for neurological therapeutics in the area of pain management (5). Low Intensity Focused Ultrasound Pulsation (LIFUP) is a relatively new medical technology platform capable of neuromodulating regions of interest of the brain with high precision. Recent studies show LIFUP as a safe and effective means for neuromodulation in pathologies such trauma and epilepsy (6-7). Additionally, focused ultrasound has been shown to induce reversible physiological effects on the nervous system, ranging from increased excitation in regions of interest to suppression of visual evoked potentials (8-9). Importantly, previous studies observed both excitation and inhibition of neuronal circuitry without characteristic physiological changes within the sonicated area such as cavitation or heat damage (10-13). Extrapolating off past studies, LIFUP may have a modulatory effect on the neuronal circuitry involved with pain, specifically when it is applied to the anterior nuclei of the thalamus, which is an important part of the pain circuit (14). Precise laboratory studies will disclose the circumstances under which LIFUP produces analgesia. The first step toward appraising LIFUP as a therapy for pain management is to determine if LIFUP produces analgesia through suppression of the anterior thalamus. Neurosurgical lesioning the anterior thalamus has been used for many years as an invasive and risky treatment for pain.

One way to diminish the risks associated with opioid analgesics is to develop therapies that reduce the dose or frequency of opiate prescriptions. Thalamic suppression via LIFUP might eventually evolve into a treatment. Regardless, this study will demonstrate a proof of concept about this new technology and its ability to influence brain circuitry and behavior. This study will be one of the first to address this limitation. On a basic science level, this study will reveal important clues about the link between regional brain activity, nociception and pain. In this sense, LIFUP is an interventional tool with which to stimulate the thalamic networks in order to evaluate its functional connections and their relevance to pain. On a clinical level, this study will contribute to the evaluation of thalamic LIFUP as an interventional tool for pain. The importance of this last goal cannot be overstated given rising opiate abuse and the extent to which chronic and postoperative pain remains undertreated (25, 26).

4.0 Study Endpoints – Overall we will test whether thalamic LIFUP during a pain provocation is safe and feasible. In addition, we will test the following endpoints.

4.1. Primary endpoint: Thalamic LIFUP will modulate pain ratings measured by administering cutaneous hot and cold stimuli via the Medoc Pathway System.

4.2. Secondary endpoints: Thalamic LIFUP will reduce BOLD activity in the thalamus.

5.0 Inclusion and Exclusion Criteria/Study Population

Screening Procedures. Prospective subjects (self-referred via flyers, e-mail announcements, and Catalyst advertisements) will be interviewed by the research team over the phone. Questions asked during this phone interview will focus on chronic (and current) medical problems, seizure history, medications, psychiatric disorders, substance abuse, magnetic resonance imaging eligibility and pain history. The inclusion/exclusion criteria will be used to screen-out participants with conditions that might interfere with or confound the research, or that might render participants vulnerable to potentially negative effects of the

laboratory pain procedures. A copy of the screening form is uploaded to the eIRB website. If the participant qualifies for the study and wishes to proceed, then he or she will be invited to a screening visit that will take place in a quiet office in the Institute of Psychiatry. The research procedures, risks and benefits will be explained during this visit. After providing written informed consent to participate, if the participant is female, then she will also receive a pregnancy test. Participants will be paid $**30** for participating in the screening procedure. Participants meeting inclusion criteria will be invited to participate in the laboratory investigation. If they choose to participate, they will be paid $**120** for Visit 2 scanning session and **$120** for Visit 3scanning session for a total of **$270**.

Selection Criteria. Participants must meet the following criteria: (1) 18-45 years of age, (2) no seizure history (individual or family), (3) no history of depression, (4) no hospitalizations or surgeries in the previous 6 months, (5) not currently experiencing pain, (6) no history of chronic pain, (7) no metal implants or objects (e.g. pacemakers, metal plates, wires), (8) not pregnant, (9) no alcohol dependence (10) no illicit drug use in the previous 6 months, (11) no known allergy to capsaicin, (12) no history of brain surgery or brain lesions, (13) no history of loss of consciousness (greater than 15 min), (14) no stimulants or medications that lower seizure threshold.

6.0 Number of Subjects – 35

7.0 Setting

The initial screening, interview, and structural scan (Visit 1) will be on the Center for Biomedical Imaging at 30 Bee Street. For Visit 2 and 3, the Brainsight targeting will occur on at the Brain Stimulation Lab on the 5th floor of the Institute of Psychiatry. The LIFUP-MRI scanning will be done at 30 Bee St.

8.0 Recruitment Methods

We will use flyers and word of mouth and email to recruit these healthy volunteers.

9.0 Consent Process

Subjects will be phone screened and then scheduled for a interview on the 30 Bee Street. There they will read the informed consent and the investigators will answer questions.

10.0 Study Design/Methods

10.1. Study Design. Twenty healthy volunteers between 18-65 years of age without history of depression or chronic pain will be recruited to participate in this sham-controlled, double-blind crossover study, all within one session within the MRI scanner. All participants will receive 10 minutes of sham LIFUP, 20 minutes of rest, and 10 minutes of real LIFUP within the MRI scanner using the BXPulsar 1001, Brainsonix Inc. The order will be counterbalanced. The duration of the LIFUP analgesia and BOLD effects will be determined.

10.2. Behavioral Measures. We will begin baseline pain assessments by administering cutaneous hot and cold stimuli via the Medoc Pathway System (Medoc, Durham, NC) using a 30 x 30 mm ATS thermode. There will be two behavioral measures: quantitative sensory testing (QST) on untreated skin and blocks of pain on capsaicin-treated skin.

QST will be done using method of limits testing on the thenar eminence of the right hand. A program will be set up to administer 10 hot stimuli with random durations between each trial. The ATS thermode begins at 32^{o}C and increases by 0.5^{o}C per second. Participants will be asked to press a button in order to signify three different measures: (1) sensory threshold, or the temperature at which the stimulus becomes noticeable, (2) pain threshold, or the temperature at which the stimulus becomes painful, and (3) pain tolerance, or the temperature at which the stimulus becomes too painful to tolerate. Measuring these thresholds will yield information about

Aβ, Aδ, and C fibers, respectively. The device will be set to stop heating at 51.5º C and stop cooling at 0º C to avoid tissue damage. These ten trials will be performed once before and once after each scanning block, either with thalamic LIFUP or 'fake' thalamic LIFUP.

Blocks of pain will be administered with an adaptation of an established heat/capsaicin model (27). First, 1% capsaicin cream will be applied to a 40 x 40 mm region of skin 12 cm away from the wrist on the right volar forearm. After 30 minutes, the capsaicin cream will be cleaned off and cutaneous heat stimuli will be applied via the Medoc Pathway System using a 30 x 30 mm ATS thermode. Pain ratings will be assessed by administering 22 s blocks of pain at a temperature that each participant reports at baseline to be 7 out of 10 on a pain visual analog scale. This temperature, individualized for each participant at baseline using the PEST procedure, will be administered throughout the experiment. Studies have shown that stimuli rated as 7 out of 10 produce highly reproducible results in terms of pain ratings and fMRI activation without posing significant risk to participants (28). The device will be set to stop heating at 51.5º C to avoid tissue damage. After each heating trial, participants will rate the intensity of the pain from 1-10. The temperature rated as "7 out of 10" at baseline will be administered 12 times during the baseline scan, 12 times during the scan following sham LIFUP and 12 times during the scan following real LIFUP. These procedures have been used previously in IRB-approved studies.

10.3. Magnetic Resonance Imaging (MRI). A Siemens 3T Trio MRI scanner will be used for imaging. After QST testing, the MR compatible ATS thermode will be placed on the capsaicin-treated right volar forearm. Participants will undergo standard high-resolution anatomical scans prior to undergoing functional scans during which 22 second blocks of heat will alternate with 22 second blocks of rest. These heat stimuli were previously rated as "7 out of 10" in intensity during baseline testing. Each fMRI scan will involve 12 pain/rest blocks. At the end of the functional scan, each participant will rate the intensity of the pain that they experienced. The functional pain/rest scan will be repeated three separate times throughout the experiment: (1) at baseline, (2) after 20 min of sham LIFUP, and (3) after 20 min of real LIFUP. A short interleaved LIFUP-fMRI scan will be performed immediately before the pain/rest block scans after sham LIFUP and real LIFUP. During these sessions, the LIFUP machine will fire single pulses at 1Hz frequency. A TR delay will be used to minimize LIFUP-induced destruction of acquired scan data. E-Prime software will be used to trigger LIFUP pulses and coordinate them with scanner TR delays. The purpose of the interleaved LIFUP-fMRI sequence is to examine how LIFUP affects BOLD signal changes in real time.

12.0 Data Management

The behavioral pain measures will be examined using a repeated measures ANOVA with time and condition (LIFUP, sham) as between group variables. These will be paired data within each subject.

Justification of Sample Size: Prior studies by our group using this same paradigm have shown differences in pain intensity with prefrontal TMS, or blocking of opiates. (29)

Consent procedures will be carried out within a private room inside the IOP. Data acquisition will be performed within the MUSC CBI research scanner at 30 Bee St. The data will not be labeled with identifiable information. Participants will be identified on all research records solely by a number, ensuring confidentiality of all data. Any information that is obtained in connection with this study and that could identify the participants will remain confidential and will not be released or disclosed without their further consent, except as specifically required by law. If the results of this research are presented at scientific meetings, participant identity will not be

disclosed. All conversations with participants will take place behind closed doors in front of only the participant and designated caregivers, family, or friends.

Any imaging or other research data will be stored in a de-identified manner.

12.1. fMRI Data Analysis: Individual fMRI Data Analysis (first level analysis): The fMRI data will be analyzed blind to LIFUP activation. MR scans will be transferred into ANALYZE format with MRIcro (http://www.sph.sc.edu/comd/rorden/mircro.html) and then further processed in Matlab 7.3 (Mathworks, Sherborn, MA) with Statistical Parametric Mapping software 12 (SPM12, The Wellcome Department of Cognitive Neurology, London, http://www.fil.ion.bpmf.ac.uk). Default settings were used unless indicated otherwise. All volumes will be realigned to the first volume. After realignment, for all subjects, movement across the 8 minutes scan must be less than 0.5 mm in 3 axes and less than 0.5 degree in 3 orientations. The images will be normalized stereotactically into a standard space with a resolution of 3 mm^3 voxels using the averaged functional EPI image – the Montreal Neurological Institute (MNI) EPI template in SPM12. Subsequently, the data will be smoothed with an anisotropic 8 mm^3 Gaussian kernel and high-pass filtered (cut-off period=128s). In a first level of statistical analysis, using a boxcar function convolved with the modeled hemodynamic response function as the basic function for the general linear model, we will obtain contrast-maps of the difference between task and rest for each subject. The six head movement parameters will be included as confounds.

Group Data Analysis (the second level analysis): Subject-specific contrasts will be entered into a second-level analysis to obtain a random effect analysis of activation effects across the entire group. The combined group *t* maps will be thresholded at $p \leq 0.05$ corrected for multiple comparisons (family-wise error, FWE) and cluster analyses will be performed with a spatial extent threshold of 5 voxels.

13.0 Safety of Subjects

We will convene a data safety monitoring board for this trial. This will be an MD psychiatrist or neurologist at MUSC and an RN familiar with Brain Stimulation but not associated with this project. This is not a clinical trial, merely a scan with ultrasound involved.

We will inform the DSMB of any SAEs promptly, and AE's with each annual renewal. In addition, after the first 10 subjects are enrolled we will summarize the AE's and SAE's, if any, and then convene the DSMB to review these and report their conclusions to the IRB. They will then review SAEs and AEs at the termination of the study.

There will be no formal DSM meetings, but the DSM board will be presented the data after 10 subjects have been scanned and then again at study completion.

All adverse events will be recorded at all visit contacts.

The supervising Institutional Review Board (IRB) will be notified of adverse events, risks, or unanticipated problems according to their reporting requirements. If any adverse events are noticed which are not described in the consent or are serious, we will inform the IRB before continuing with the next enrolled subject. Data collected regarding serious adverse events will include the dates of the scan and the AE and presumed relationship to study stimulation and will be updated as new information becomes available; a narrative description also will be provided.

15.0 Risks to Subjects

fMRI, EEG measures:

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. There is also a risk if the subject is pregnant but we will exclude pregnant subjects.

LIFUP stimulation:
When used at/below intensities deemed safe by the FDA, no significant and persisting side-effects have been reported, as confirmed in healthy volunteers (Legon et al., 2014), brain injury patients (Monti et al., 2016; see also Interim report on safety enclosed in this application) as well as non-human primates (Deffieux et al., 2013), and other animal models (Tufail et al., 2010; Tufail et al., 2011).
In addition, although in the context of a different study, the FDA has granted to the device we will use a status of Category B (that is, safe and effective) Investigation Device Exemption (G130290), on 2/12/2014. Indeed, this is consistent with the known physics and biophysics of our stimulation protocol in which the device is operated at (acoustic) energy levels that are (1) well below those of a typical Pulsed Doppler ultrasound conventionally used in the clinical context in adults and children (by around 40%), and (2) within the energy limits deemed safe by the FDA.

Thermal Pain System: The Medoc pain system has been used safely by Dr. Borckardt and others for over a decade now. The pain is unpleasant but there are limits to the amount of pain, and there have been no adverse events over 5 MUSC IRB approved studies.

16.0 Potential Benefit to Subjects
These are healthy volunteers and this is a single scan and there is thus no potential benefit to the subjects.
The risks to subjects are reasonable however with respect to the potential benefit of developing a new brain stimulation method that is superior to the status quo in terms of being able to stimulate deep in the brain, noninvasively, and focally.

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