PROTOCOL TITLE:

Evaluating the effects of transcranial focused ultrasound (tFUS) on fronto-striatal resting state functional connectivity in healthy individuals

PRINCIPAL INVESTIGATOR:

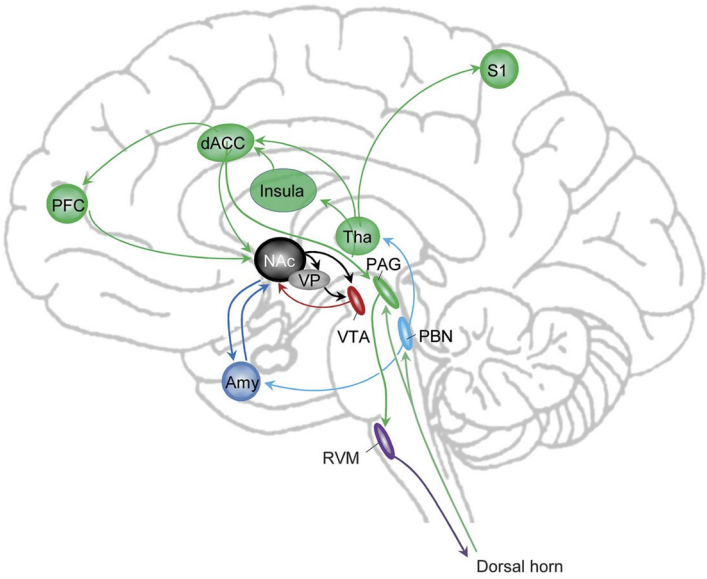
- Bashar Badran, PhD

1.0 Objectives / Specific Aims

Aim: Evaluate whether sonicating the Nucleus Accumbens (NAc) with transcranial focused ultrasound modifies functional connectivity between the NAc and the prefrontal cortex (PFC).

In this single visit, open-label pilot trial, we plan to evaluate whether transcranial focused ultrasound (tFUS), delivered to the nucleus accumbens (NAc) within the magnetic resonance imaging (MRI) scanner will impact resting state functional connectivity between the NAc and functionally connected brain regions like the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC) in up to 10 healthy individuals.

HYPOTHESIS : tFUS will reduce prefrontal cortex (PFC)-NAc functional connectivity, in healthy individuals. We will investigate this hypothesis by administering tFUS within to MRI scanner to healthy individuals and conduct resting state functional neuroimaging before- and after the tFUS stimulation.



Functionally connected areas of the Nucleus Accumbens (NAc). Key emotional, pain, and reward systems are connected through the NAc, including the insula, dorsal anterior cingulate cortex (dACC), prefrontal cortex (PFC), thalamus (Tha), amygdala (Amy), and periaqueductal gray (PAG). Additionally, the NAc receives excitatory inputs from the ventromedial PFC, dACC, amygdala, and hippocampal formation (not shown) and dopaminergic inputs from the ventral tegmental area (VTA) of the midbrain.

2.0 Background

Currently, several brain stimulation approaches have attempted to modulate pain, mood, and behavior with limited success. The two most studied approaches are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). 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. Unlike TMS, which is a cortical stimulation approach, deep brain stimulation (DBS), which is FDA approved for treating Parkinson's Disease (PD), can stimulate deep in the brain with high spatial specificity. DBS has been also investigated experimentally to manage neuropathic pain; however, the surgical risk and implantation of the electrodes are semi-permanent and arguably not worth the benefit. Lastly there is tDCS, a low cost, low-amplitude electric current delivered to the scalp and ultimately through brain. tDCS is not powerful enough to depolarize neurons, although it has been demonstrated to influence the level of excitability and modulate the firing rate of individual neurons. Of all brain stimulation approaches, there is a need for a safe, noninvasive, focal, and effective approach that can reliably modulate neural tissue. This proposal addresses this gap, by advancing transcranial focused ultrasound (tFUS), a technological advancement on the forefront of neuroscience and neuromodulation (**Figure 2**).

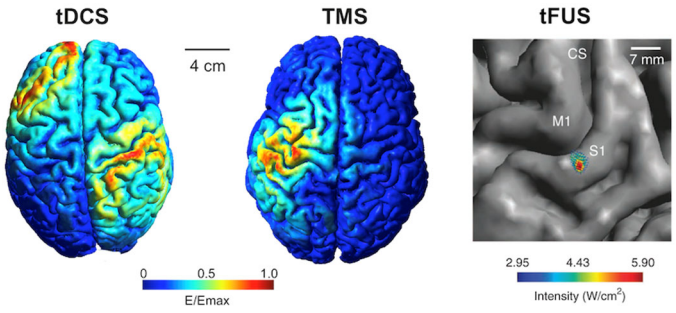


Figure 2. On the right, the electric fields produced by tDCS and TMS are presented. These two commonly utilized forms of brain induce biologically active electrical fields in broad (>4cm) cortical targets. Alternatively, tFUS (right) has the capability to focally deliver energy to cortical and subcortical tissue with <1cm resolution.(33)

This open-label pilot study is investigating the basic underlying mechanism of tFUS, and evaluating whether this technology can stimulate deep brain structures associated with reward, pain, and addiction – the nucleus accumbens. We aim to use resting state neuroimaging to understand what happens to functional neural circuitry of connected brain structures to the site of stimulation.

3.0 Intervention to be studied (if applicable)

Transcranial Focused Ultrasound (tFUS)

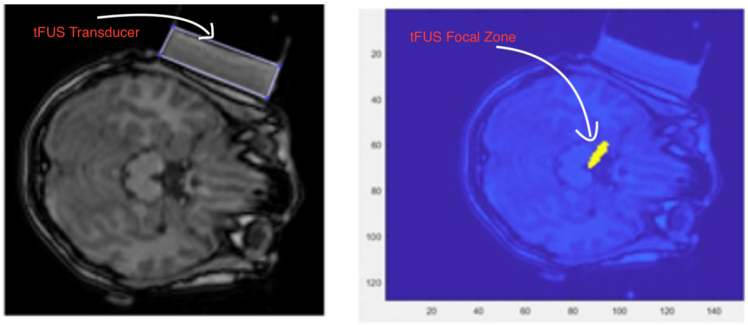


Figure 3. Screenshots from our custom-made software (47) used to show the tFUS transducer (left) placed on the scalp, and (right) the theoretical peak sonication area deep within the brain based on the fixed focal length of the specific transducer used.

Transcranial focused ultrasound (tFUS) is a promising new technology that is both noninvasive and may be focally applied to deep brain targets(1-4) (**Figure 3**). tFUS utilizes transducers which contain piezoelectric elements to produce pulses of ultrasonic waves that summate deep in the brain(5-7). tFUS noninvasively stimulates deep brain targets with a high level of spatial resolution. No other current technologies exist for noninvasive deep brain stimulation which makes tFUS a highly promising technology that may have substantial research and clinical potential(1, 4, 8-12). Transcranial focused ultrasound (tFUS) uses a single large concave transducer fixed in a head-worn apparatus on the scalp to produce ultrasonic waves (650kHZ) pulsed in 30 second intervals. Unlike traditional diagnostic ultrasound, which constantly transmits ultrasound and 'listens' to the echo to form an image, tFUS delivers the ultrasound in trains or short bursts of pulses. It is still unclear whether tFUS, at the FDA-prescribed power limits, depolarizes neurons, however is hypothesized that tFUS acts on neurons via a mechanical force mechanism of action, leading to increased conductance of neurons and opening of ion channels(13).

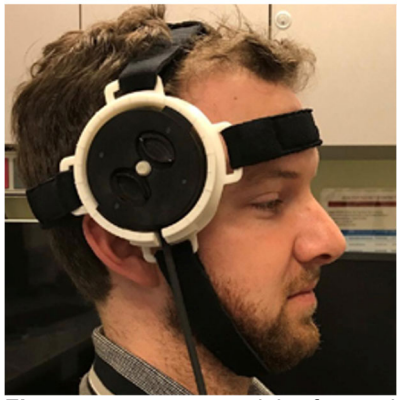


Figure 4. transcranial focused ultrasound (tFUS) holder system containing the tFUS transducer.

Due to the inherent fundamentals of the waveform of ultrasonic forces, tFUS maximal energy can be focused both deep in the bran (2-12cm under the cap; for comparison, traditional TMS can stimulate 1-3.4cm^2 deep(14, 15)) 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 50mm^2 (14, 15)). Furthermore, tFUS has been demonstrated to safely stimulate neural tissue(12, 16-18), proposing cellular mechanisms for its efficacy(12, 18-23), and now is being used in human patients(24). Recently, tFUS administered to the thalamus of coma patients was demonstrated to assist in recovery of consciousness(24). Thus, tFUS is an extremely promising, new form of noninvasive deep brain stimulation that can be focused on deep brain structures to elicit meaningful behavioral responses. This proposal plans to use tFUS, administered to deep brain structures involved in reward and pain, to produce changes in brain functional connectivity.

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.

Attached is the letter 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.

Additionally, the MUSC IRB1 has approved this system to investigate a new potential treatment for pain, which was shown to be safe at the proposed parameters and published recently(25). Additionally there is an ongoing trial using the same system (PI George) approved the IRB 1 in generalized anxiety disorder.

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.

In this study, up to 10 participants will receive two, 10minute sessions of either active or sham tFUS delivered to the nucleus accumbens (NAc) within the MRI environment.

4.0 Study Endpoints (if applicable)

Primary Outcome: Neuroimaging/Fronto-Striatal Resting State Functional Connectivity

The main outcomes of this study are brain imaging related. Using a neuroimaging technique called resting state functional connectivity, which is a statistical dependence between time series of electro-physiological activity and (de)oxygenated blood levels in distinct regions of the brain. Functional connectivity "strength calculation" determines whether the activity between a pair of brain regions covaries or correlates over time. We will investigate the strength of the functional connectivity between the stimulation target (Nucleus Accumbens) and connected areas, including the prefrontal cortex, hippocampus, amygdala, and sensory areas of the brain at baseline, and then will determine whether tFUS increases or decreases the resting-state connectivity between these regions after the NAC has been stimulated.

5.0 Inclusion and Exclusion Criteria/ Study Population

Healthy volunteers of all ethnic and racial categories will be accepted into this study protocol. No preference will be given based on race, gender, or ethnicity. Pregnant persons and children under the age of 18 will be excluded for safety reasons. No vulnerable populations or special classes of subjects will be considered for participation.

Inclusion Criteria

- Age 18-65
- Have the capacity and ability to provide one's own consent and sign the informed consent document

Exclusion Criteria

- Contraindicated for MRI.
- Any current or recent untreated medical, neurological, or psychiatric conditions
- Metal implant devices in the head, heart, or neck.
- History of brain surgery.
- History of myocardial infarction or arrhythmia, bradycardia.
- Personal or family history of seizure or epilepsy or personal use of medications that substantially reduce seizure threshold (e.g., olanzapine, chlorpromazine, lithium).
- Personal history of head injury, concussion, or self-report of moderate to severe traumatic brain injury.
- Individuals suffering from frequent/severe headaches.
- Individuals with a reported history of psychosis or mania, or individuals who are actively manic or psychotic.
- Regular or recent pain medication use
- Moderate to severe alcohol use (>3 drinks/day) or illicit substance use (urine confirmed).
- Persons who are pregnant or lactating

6.0 Number of Subjects

We will enroll up to 10 healthy adults for this study.

7.0 Setting

All participants will complete the study tasks on at the MUSC 30 Bee Street Center for Biomedical Imaging. Subjects will be consented and educated about the study in a private screening area within the 30 Bee Street center. tFUS will be administered within the MRI scanner.

8.0 Recruitment Methods

Healthy participants will be recruited from the MUSC community (students and staff) as well as general population from the greater Charleston region. We will recruit via word of mouth and flyers.

9.0 Consent Process

Consent procedures will be conducted in a private, quiet room at the MUSC 30 Bee Street Center for Biomedical Imaging. Approved study personnel will walk through the consent procedures with the participant. Furthermore, after the consenting procedures, the consent form will be printed and provided to all participants to independently review to ensure understanding, including describing the laboratory measures, study duration, and equipment and materials. The study team will describe confidentiality/privacy measures, participant right to withdraw, risks/benefits, and that up to $100 compensation will be provided. In addition, participants will be prompted to ask questions throughout consenting to further ensure understanding. After signing the consent form, they will also be offered a hard copy.

10.0 Study Design / Methods

- *Study Overview:* After determining eligibility and interest, written informed consent will be obtained from participants at the MUSC Center for Biomedical Imaging. Enrolled participants will be placed into the 3T MRI outfitted with a concurrent tFUS plus fMRI acquisition system (Brainsonix). First, participants will have baseline resting state functional neuroimaging conducted to quantify the functionally connected areas to the nucleus accumbens. Afterwards, while still in the MRI scanner, we will administer tFUS to the nucleus accumbens. Lastly, we conducted post-tFUS neuroimaging (same as pre-tFUS). This entire MRI procedure will take approximately 1 hour. Participants will be compensated $100 for their time.
- *Recruitment, Screening, and Consent Procedures:* Healthy participants will be recruited from the MUSC community (students and staff) as well as general population from the greater Charleston region. We will recruit via flyers around campus, e-mail announcements and word of mouth. If interested in learning more about the study, potential subjects will be phone screened and educated regarding the study's details. If interested in participating in the study, they will be consented and enrolled into the study's protocol. We then will conduct a multi-panel urine drug screen to confirm they are not using illicit drugs and ask for their alcohol consumption (>3 drinks per day is exclusionary).
- *Pregnancy Test Procedures:* If participants are individuals biologically capable of becoming pregnant, they will be provided with a pregnancy test strip After completing the pregnancy test, participants with negative results will be asked to continue to the remaining study procedures, whereas those with a positive result will be debriefed and released.
- *tFUS Procedures:* All tFUS will be administered in similar mythology to that in our prior published work (25). Within the MRI scanner, participants receive two, 10-min sessions of either active or sham tFUS spread 10 min apart targeting the nucleus accumbens [fundamental frequency: 650 kHz, Pulse repetition frequency: 10 Hz, Pulse Width: 5 ms, Duty Cycle: 5%, Sonication Duration: 30s, Inter-Sonication Interval: 30 s, Number of Sonications: 10, ISPTA.0 995 mW/cm2, ISPTA.3 719 mW/cm2, Peak rarefactional pressure 0.72 MPa].
- *Sham tFUS Procedues:* Participants will be randomized to receive either two, 10 minute active tFUS sessions, or two 10 minute sham tFUS sessions within the scanner. The sham sessions will include a transducer that is connected in a similar fashion to that of active tFUS, however the cable will not be plugged into the system, thus no ultrasound will be delivered to the participant. Participants will not know or be told whether they are receiving active- or sham- tFUS.
- *Neuroimaging Procedures:* All MRI imaging will be performed using a Siemens 3.0 T Prisma scanner equipped with a 32-channel head coil. MRI data will be acquired from all participants before and after tFUS administration. All MRI scan visits will be held at the MUSC Center for Biomedical Imaging (CBI; see the Facilities and Resources section). Each MRI scan session will include a high-resolution T1-weighted structural scan (whole brain sagittal acquisition, 224 slices, TR=2530ms,

TE=3.65ms, TI=1100ms, 1mm thick slices, FOV=256, 256x176, flip angle = 7 degrees.), followed by 24 minutes of resting-state scanning, then a concurrent tFUS/fMRI paradigm, and lastly, 24 more minutes of post-tFUS resting-state scanning. All functional scans will use the high-resolution fMRI protocol described in the Preliminary Study: whole brain acquisition, 136 axial slices, 1.5x1.5x1.5mm voxel size, TR=2000ms, TE=30ms, FOV=204mm, multi-band factor=3.

12.0 Data Management

All data will be stored in the Redcap database as well as in paper documentation. Information about the participant (including their identifiable private information) may have all their identifiers removed and used for future research studies or distributed to other researchers for future research without additional informed consent. After participation, RedCAP data will be downloaded in excel format to the secure MUSC server. Paper documentation will be stored in locked cabinet within a locked office of the study team. In terms of publication, data will be published in aggregate form, so individual participants will not be identifiable in the final manuscript. No identifying information will be published.

Neuroimaging data will be collected from the 3T MRI scanner at 30 Bee Street. All imaging data will be automatically transferred to and stored on a password-protected, encrypted secure server that limits data access to personnel directly involved with the study. The data will be analyzed using standard imaging analysis software packages such as FSL and SPM.

Confidentiality and Quality Control: All study personnel will complete Social-Behavioral-Educational research CITI training, and also complete in-lab training regarding data security practices. Study personnel will be trained in the IRB protocol. The investigator, and co-investigators will be available to monitor data collection to ensure quality, confidentiality, and adherence to the IRB protocol.

The study's procedures will take place at the MUSC 30 Bee Street Neuroimaging. Regarding documentation, participant names will appear only on the IRB-approved Consent and HIPAA. Patients will be receiving tFUS within the MRI scanner and they will be aware of this information prior to choosing to participate.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

There are three areas in which safeguards to protect subjects from undue risk require discussion. These Include: (1) procedures used to obtain informed consent, (2) procedures used to ensure confidentiality of the subject data, and (3) procedures used to minimize possible risks associated with the laboratory procedures. Regarding informed consent, participants are fully advised on the research procedures to be used, the amount of time required of them, the possible risks and benefits of the procedures, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the principal investigator. All subjects will be required to have capacity to consent. Regarding confidentiality, subjects are informed that the information they provide will be kept strictly confidential, with access limited to the research staff. Participation in the study will be treated as confidential, as will all records. The identity of subjects will be protected with alphanumeric codes. All data will be kept in locked file cabinets file cabinets or on secure servers designed for use and access by study team only.

We do not anticipate any adverse events to occur in this study, however the experienced research team has a long-standing record of recording and reporting unanticipated adverse events to the IRB. We will report any adverse event within 48 hours to the IRB.

14.0 Withdrawal of Subjects

Participants will be informed during consenting that they are free to withdraw from the study at any time. They will be informed that they are not obligated to participate once the study is initiated and in particular will be reminded prior to tFUS stimulation and neuroimaging that they may discontinue stimulation and/or the experiment at any point.

15.0 Risks to Subjects

tFUS 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(11), brain injury patients(7)as well as non-human primates(26).

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.

Safety in case of pregnancy
We do not know if the study drug will affect mother's milk or an unborn fetus. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. If you are pregnant or become pregnant, there may be risks to the embryo or fetus that are unknown at this time. Women who can become pregnant must take a pregnancy test before the start of the study.

You should not father a child while on this study as the treatment may indirectly affect an unborn child. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use a method to avoid pregnancy that works well or you must not have sex.

Unless you cannot have children because of surgery or other medical reasons, you must be using an effective form of birth control before you start the study. You must also agree to continue to use an effective form of birth control for 2 month/s after taking the study drug.

Magnetic Resonance Imaging (MRI):
MRI tests are non-invasive. There are no known risks or side effects associated with conventional MRI procedures except to those people who have electrically, magnetically or mechanically activated implants (such as cardiac pacemakers) or to those who have clips on blood vessels in their brain. There are no known additional risks for combined tFUS+fMRI procedures. However, an MRI may cause you to feel claustrophobic (uncomfortable in a small space) or anxious from the noises made by the machine.

Unknown Risks:
There is always the possibility of other risks for a relatively new technology. The Study team will let the participant know if they learn anything that might make the participant change their mind about participating in the study.

Loss of Confidentiality:
There is a risk of a loss of confidentiality of personal information. Subjects are informed that the information they provide, as well as participation in the study, will be kept strictly confidential, with access limited to the research staff. The identity of subjects in databases will be protected with alphanumeric codes. All data will be kept in locked file cabinets or on secure servers designed for use and access by Study Team members only.

16.0 Potential Benefits to Subjects or Others

There will be no direct benefit to the participant in the study. Data from this study, however, will benefit society by improving the understanding of if and how tFUS affects brain function and potentially work towards developing a novel therapeutic device.

17.0 Sharing of Results with Subjects

There is no plan to inform subjects of the results of the study, but they can always contact the research staff and ask. If there are significant new findings during the study, they will be notified.

18.0 Drugs or Devices

Brainsonix 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 is the same in terms of what they can produce.

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