CONSENT TO PARTICIPATE IN RESEARCH

Title: Transcranial ultrasonic neuromodulation of primary visual cortex and primary auditory cortex in human

You have been asked to participate in a research study conducted by Daniel Freeman, Christopher Smalt, and Jeremy Kemmerer, from the Advanced Technology Division and Biological Engineering Division at the Massachusetts Institute of Technology (M.I.T.) Lincoln Laboratory. This study is sponsored by the Office of Undersecretary of Defense (OUSD) in the Department of Defense.

You were selected as a possible participant in this study because you are an adult in good health without a history of neurological or psychiatric illness. We expect 20 people will be in this research study.

The information below provides a summary of the research. Your participation in this research is voluntary and you can withdraw at any time.

- **Purpose:** To investigate how and whether ultrasound waves delivered to your brain through the skull may temporarily excite or suppress the activity of a brain region that is related to the sensory processing vision and hearing.
- **Study Procedures**
  The study will involve three different in-person visits. In the first and third visit, to MIT McGovern Institute (Cambridge, MA), you will get an MRI scan and be asked to perform a simple visual or hearing task. In the second visit, to MIT Center for Clinical and Translational Research (CCTR) (Cambridge, MA), you will again be asked to perform a simple visual or hearing task, and additionally, there will be low-intensity ultrasonic signals applied through the skull to a sensory area of your brain while we record electrical signals from your scalp.
- **Risks & Potential Discomfort**
  We anticipate minimal risks and discomfort associated with this study. MRI scans are safe, and if you feel uncomfortable, there will be a push-button to alert the staff, and you can leave the scanner upon request. On a separate visit, we will also deliver low-intensity ultrasonic waves through the skull to influence brain activity using intensity levels approved by the FDA. More details of the associated risks are described below.

Your participation in this research is completely VOLUNTARY. You should read the information below, and ask questions about anything you do not understand before deciding whether or not to participate.

- **PURPOSE OF THE STUDY**

This study involves the use of an investigational device referred to as transcranial ultrasound, which uses ultrasonic waves delivered through the skull to the brain to cause small changes in activity of neurons. The purpose of this study is to evaluate whether the ultrasound stimulus will temporarily excite or suppress the activity of a brain region that is related to the sensory processing vision and hearing. Although the excitation or suppression of the sensory areas of the brain may not have beneficial effects, the information we learn from the study may someday be used to modulate the function of other brain areas in people having neurological disorders, such as chronic pain and major depression. The ultrasound hardware system we will use are commercially available, made by the companies Openwater and Attune. These devices are not approved diagnostic or therapeutic use by the U.S. Food and Drug Administration (FDA). The systems are considered investigational and will be operated under the oversight of MIT's Institutional Review Board (IRB), COUHES.

The purpose of the study is to evaluate whether transcranial ultrasound can controllably alter the neural activity in sensory cortex. The ultrasonic hardware is affixed to the head of the subject using Velcro straps, and gel will be applied to the skin to facilitate acoustic stimulation. This ultrasonic transducer will apply acoustic signals through the skull to cause minute vibrations in neural tissue that can modulate brain activity. The resulting of the modulation in brain activity can be measured in multiple ways: (1) with electrical recordings from electrodes on the scalp, or (2) through visual or auditory perceptual effects that can be reported by the subject . This device has been used in prior human studies and has been approved by Institutional Review Boards (IRB) in the United States. Details of the specific IRBs and universities involved, as well as study findings, are available upon request to the PI.

- **PROCEDURES**

If you volunteer to participate in this study, we would ask you to do the following experimental procedures:

Visit 1 – Consent, MRI, and Baseline Visual or Auditory Testing (Total time about 2 hours)
MIT McGovern Institute (43 Vassar Street, Cambridge, MA).
The PI and/or a co-investigator will again conduct a review of whether you are eligible for enrollment. Assuming you are eligible and you decide to continue your participation in the study, we will conduct a brief (~10 – 15 minute) exam to assess the performance of your visual or auditory system. Then, you will be asked to undergo an MRI scan, where you remove all jewelry and other metals from your person, you will be provided with a garment to change into, and you will be instructed to lay down on the scanner bed. This scan will be conducted in order to obtain anatomical and functional information about your brain areas that represent visual or auditory system. During the scan, you will be able to communicate with the technicians either verbally, through a built-in communication system inside the scanner, or through a push-button that is available for alerting the staff of any discomforts or other problems.

Visit 2 – **Ultrasound Session (Total time about 3 hours)**
MIT Center for Clinical and Translational Research (45 Carleton Street, Cambridge, MA)
In this visit, you will receive testing of the ultrasound system, which will apply low-intensity acoustic signals to your brain. The date of this test will be determined based on how long it takes us to prepare your data from the prior session but will be kept within two weeks from Visit 1. Please avoid an excessive amount of alcohol intake (for example, no more than one can of beer or a glass of wine) or strenuous exercise (no more than your daily routine) on the day of the visit. If you do not comply with these directions, then the visit may be postponed. If this happens more than once, then the participant may be removed from the study. We will conduct a brief (~10 – 15 minute) exam to assess performance of your visual system or auditory system. This is the same test that was conducted during Visit 1. Next, you will put on the headgear that has an ultrasound device embedded inside. EEG sticker electrodes will be applied at several positions on your scalp to measure brain electrical activity. Some based gel will be applied between the ultrasound transducer and the scalp to provide uninterrupted sound transmission. We will obtain EEG to measure electrical activity of your brain resulting from ultrasound stimulation and from visual stimulation (e.g., a flash of light, or image of an object or face) or auditory stimulation (e.g., a tone played from the speaker, or white noise). At the end of the ultrasound session, you will be asked to provide a description of the visual or auditory sensations you perceived. We will administer the visual or auditory exam, as was performed at the beginning of this visit. You will remain on the premises for at least 30 minutes for monitoring and will be accompanied by a research staff member.

Visit 3 – **MRI and Visual or Auditory Testing (Total time about 1.5 hours)**
MIT McGovern Institute (43 Vassar Street, Cambridge, MA).
In this visit, we will perform the final round of testing of visual and auditory performance. This will be scheduled to occur at least 1 week after Visit #2. Additionally, during this visit, we will perform an additional MRI scan.

Participants can opt-out of being contacted for future research by calling Daniel Freeman (617-877-7145)

- **POTENTIAL RISKS AND DISCOMFORTS**

Ultrasound-Related Risks and Discomforts
The ultrasound hardware used in this study was developed by the companies Openwater (for visual sonication, model number Open-LIFU 3.0) and Attune (for auditory sonication, model number ATTN201). Your permission will be obtained to operate the system. The risks involved with ultrasound application to the brain are (1) heat-related damage if the energy of ultrasound yields excessive temperature increase and (2) mechanical damage, especially by the phenomenon called cavitation, which refers to the expansion/contraction or the collapse of bubbles inside biological tissue due to ultrasound. Because the acoustic pressure waves will be given at a low intensity, the possibility of tissue damage is highly unlikely. However, to minimize the risk of mechanical damage, we will monitor for the presence of potential cavitation by applying a sensor to your forehead and will cease the procedure immediately if such an event is detected.

No serious adverse events have been reported in healthy human participants when parameters remain within consensus safety recommendations. Mild, transient symptoms have been described (e.g., headache, scalp sensations, sleepiness, neck discomfort, brief anxiety or trouble concentrating). Precise rates are not consistently reported across all studies, but the largest published human survey to date asked 120 participants from seven ultrasound experiments to complete a follow-up symptom questionnaire; 64 responded. None reported serious events. 7 out of 64 respondents (~11%) reported mild to moderate symptoms they felt were "possibly" or "probably" related to the ultrasound (neck pain, attention problems, muscle twitches, anxiety). Initial reports of mild neck pain, scalp tingling, and headache resolved on follow-up, and no new symptoms appeared up to one month later. Any technique that modulates brain activity carries a theoretical risk of provoking a seizure. To date, no seizures have been reported in ultrasound neuromodulation studies of healthy volunteers.

This research may involve risks to you that are currently unforeseeable. Studies have indicated that effects of ultrasound, which may include slightly reduced visual or auditory sensation, may last about 30 minutes. In addition, it is also possible that we may unintentionally apply ultrasound to a brain area adjacent to the intended location. It is difficult to know the exact outcome of this missed application; if you feel any unusual sensations, please inform the investigators. You may develop minor and temporary skin irritation at the site of contact from the water-based gel or acoustic coupling material (polyvinyl alcohol; a material used for common household plastic bags). If you have a known allergy to this material, please inform the investigator.

MRI and EEG-Related Risks and Discomforts

The MRI is a Food Drug Administration (FDA) - approved medical device. No serious or lasting incidents or side effects associated with their use have been reported. The major discomforts of the MRI are noise (proper ear-protection will be provided) and claustrophobia (feeling very uncomfortable in closed spaces). Additionally, you may feel a slight warmth or tingling sensation in your nose or extremities. However, these will not pose any threat to your health.

MRI systems use magnets to make images. Therefore, persons with metal implants, electronic devices, such as pacemakers and surgical clips, or any metallic fragments in the body should not have an MRI. Otherwise, there are no known health risks associated with this exposure. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. The MRI system makes loud banging noises as it takes images. Earplugs will be used to reduce the noise. The MRI can be stopped at any time at your request. You can make the request easily by pressing a bulb provided for you. The system used for monitoring physiological parameters such as the heart rate and respiration rate is a commonly used device. It is safe, non-invasive, and will cause little to no discomfort.

The types of MRI scans obtained in this research are not designed to look for clinical abnormalities in the structure of the brain. However, all structural scans will be reviewed by a

neuroradiologist, and if any potentially significant abnormalities are noted, you will be contacted and a recommendation for appropriate follow-up will be supplied. We will also notify your primary care doctor and recommend referral to an appropriate in-plan physician for clinical evaluation and treatment. No information generated in this study will become part of a hospital record, but if the study detects an abnormality in your MRI scan, then this information may become part of a hospital record. It is possible that you could be unnecessarily worried if a problem were suspected, but not actually found.

- **ANTICIPATED BENEFITS**

There are no direct benefits to you from taking part in this research study. We hope this information will help us learn how ultrasound can be used to non-invasively excite or suppress localized brain activity. This could help in future clinical studies that use transcranial ultrasound to treat conditions such as chronic pain and major depression.

- **PARTICIPATION AND WITHDRAWAL**

Your participation in this research is completely VOLUNTARY. If you choose to participate you may subsequently withdraw from the study at any time without penalty or consequences of any kind. If you choose not to participate, that will not affect your relationship with M.I.T. or your right to healthcare other services to which you are otherwise entitled.

Consequences of Withdrawal

You can stop taking part in this research study at any time; it will not be held against you. If you choose to withdraw, your data up until the point of withdrawal will be retained as part of the study records. No additional data will be collected from you for this study. If you stop being in the research, already collected data may not be removed from the study database. We may also consult with public records for safety reporting. For any questions, please contact the study investigator, Daniel Freeman (617-877-7145).

Withdrawal of participation by the investigator

The investigator may withdraw you from participating in this research if circumstances arise which warrant doing so. The decision may be made either to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate.

If you experience any of the following during your participation: headaches, neck discomfort associated with wearing the ultrasound device, or other unanticipated discomforts, or if you are unable to follow procedures required by the research, you may have to drop out, even if you would like to continue. The investigator, Daniel Freeman, will make the decision and let you know if it is not possible for you to continue.

The research team will not be able to delete your data already collected as part of your participation before the required data retention period. This includes photographs, video or audio recordings. After the required data retention period has passed, the research team will delete any data upon your request if it is feasible

ALTERNATIVES TO PARTICIPATION

You can choose to participate or NOT in the study and you can stop involvement in it at ANY MOMENT. The alternative to participating is not to participate and, when appropriate, to continue with the standard of care determined by the subject's physician.

- **PAYMENT FOR PARTICIPATION**

If you agree to take part in this research study, we will pay you $300 for your time and effort. Payment will be pro-rated at $100 per visit in case you do not complete the series of 3 visits. If you complete the required 3 visits to the test site, you shall receive a total payment of $300. You are responsible for arranging your own transportation to/from the testing site.

Legally, you can be paid only if you are a US citizen, a legal resident noncitizen (e.g., possess a "green" card), or have a work eligible visa sponsored by the paying institution.

If you must drop out because the investigator asks you to or because you have decided on your own to withdraw, you will be compensated in accordance with the payment for participation described above.

- **POSSIBLE COMMERCIAL PRODUCTS**

We may use your data to inform the developing of new products or medical testing to be sold. The sponsor, MIT Lincoln Laboratory, and researchers may benefit if this happens. There are no plans to pay you if your data is used for this purpose.

- **FINANCIAL OBLIGATION**

Taking part in this study will not lead to any added costs for you. However, researchers will not pay you for your travel or the time. Neither you nor your insurance company will be billed for your participation in this research.

- **PRIVACY AND CONFIDENTIALITY**

The following will know that you are a research participant and may inspect your study records:

- Members of the research team which might include outside collaborators not affiliated with MIT.
- Authorized MIT representatives to ensure compliance with MIT policies and procedures.
- Authorized representatives of the Food and Drug Administration
- Authorized representatives of a federal funding agency at the Department of Defense (Office of Undersecretary of Defense)

- Federal agencies, state agencies, and foreign government bodies that oversee, evaluate, and audit research, which may include inspection of your records
- Public health and safety authorities, if we learn information that could mean harm to you or others (such as to make required reports about communicable diseases or about child or elder abuse)
- Department of Defense may access records to ensure subject protection (32 CFR 219.116 (b)(5)) and to ensure regulatory compliance (DoDI 3216.02, para. 3.15.c). No information about you, or provided by you during the research will be disclosed to others without your written permission, except: if necessary to protect your rights or welfare, or if required by law.
- Your physicians and nurses for the purposes of medical evaluation (e.g., accessing radiological scans)

No information about you, or provided by you during the research will be disclosed to others not listed above without your written permission unless otherwise specified in this consent form, except: if necessary to protect your rights or welfare, or if required by law.

All data will be stored on a secure computer system at MIT Lincoln Laboratory on folder that can be accessed only by the research staff conducting this study. All data will be de-identified and cannot be connected back to the participant without the use of an identification code that will be stored under a password protected folder managed by the Principal Investigator, Daniel Freeman. The identification codes will be stored for a period of 5 years and then will be destroyed. All of the data from the study, including imaging scans, EEG data, and other study results will be kept indefinitely, but will not have any identifiable information.

When results of the research are published or discussed in conferences, data may include de-identified, individual-level data.

You have the right to review your data, including photographs or recordings, at any time before your completion of this study. When your participation is complete and data analysis has concluded, the research team's ability to honor your request to review your data is limited. All such requests will be reviewed on a case-by-case basis. The research team will not be able to delete your data already collected as part of your participation before the required data retention period. This includes photographs, video, or audio recordings. After the required data retention period has passed, the research team will delete any data upon request if it is feasible.

If photograph, videos, or audio recordings of you will be discussed in conferences or used for educational purposes, your identity will be protected or disguised. Any identifying features (such as your face or voice) will be shielded or disguised from photographs, videos or audio recordings before such use.

Please add your initial and date if you give permission for your photograph, audio or video to be recorded for this study. Initial _____ Date_____

A description of this clinical trial will be available on http//www.ClinicalTrials.gov, as required by U.S. Law. This website will not include any information that can identify you. At most, the website will include a summary of the results. You can search the website at any time.

- **FUTURE DATA USE**

Your non-identifiable data (e.g., MRI and EEG results collected as part of the research) will not be shared with other researchers for future research studies without additional informed consent from you or your legally authorized representative. Your data might be shared with as part of academic conferences or journals.

Traditionally used identifying information about you such as your name, address, phone number, medical record, social security number, your identifiable features or your voices, etc. will be removed before using or distributing for future research

- **NEW FINDINGS**

During the course of the study, you will be informed of any significant new findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation, that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study may be re-obtained.

- **EMERGENCY CARE AND COMPENSATION FOR INJURY**

If you feel you have suffered an injury, which may include emotional trauma, as a result of participating in this study, please contact the person in charge of the study as soon as possible.

In the event you suffer such an injury from the direct result of your participation in this study, M.I.T. will provide itself, or arrange for the provision of, emergency transport or medical treatment, including emergency treatment and follow-up care, as needed, and reimbursement for such medical services not covered by your insurance. M.I.T. does not provide any other form of compensation for injury, however, you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

You will be financially responsible for any services received for any injuries determined not to be directly related to your participation in the study.

- **IDENTIFICATION OF INVESTIGATORS**

In the event of a research related injury or if you experience an adverse reaction, please immediately contact one of the investigators listed below. If you have any questions about the research, please feel free to contact the Principal Investigator.

Daniel Freeman (Principal Investigator, Daniel.Freeman@ll.mit.edu): 617-877-7145
Christopher Smalt: 781-981-4186
Jeremy Kemmerer: 781-981-0817

- **RIGHTS OF STUDY PARTICIPANTS**

You are not waiving any legal claims, rights or remedies because of your participation in this research study. If you feel you have been treated unfairly, or you have questions regarding your rights as a study participant you may contact the Chairman of the Committee on the Use of Humans as Experimental Subjects, M.I.T., Room E25-143B, 77 Massachusetts Ave, Cambridge, MA 02139, phone 1-617-253 6787.

SIGNATURE OF RESEARCH PARTICIPANT OR LEGAL REPRESENTATIVE

I have read (or someone has read to me) the information provided above. I have been given an opportunity to ask questions and all of my questions have been answered to my satisfaction. I have been given a copy of this form.

BY SIGNING THIS FORM, I WILLINGLY AGREE TO PARTICIPATE IN THE RESEARCH IT DESCRIBES.

_____
Name of Participant

_____
Name of Legal Representative (if applicable)

_____ _____
Signature of Participant or Legal Representative Date

SIGNATURE OF PERSON OBTAINING INFORMED CONSENT

I have explained the research to the participant or his/her legal representative, and answered all of his/her questions. I believe that he/she understands the information described in this document and freely consents to participate.

_____
Name of Person Obtaining Informed Consent

_____ _____
Signature of Person Obtaining Informed Consent Date (must be the same as above)

SIGNATURE OF WITNESS (If required by COUHES)

☐ This section is required

My signature as witness certified that the participant or his/her legal representative signed this consent form in my presence as his/her voluntary act and deed.

_____
Name of Witness

_____ _____
Signature of Witness Date (must be the same as above)