Ultrasonic Deep Brain Stimulation During Anesthetic Sedation

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General Goal

The goal of this study is to understand the neural basis of human consciousness and its modulation by anesthetic agents supported by Departmental Research Funds. The fundamental question is how the state and contents of consciousness are intertwined in the brain. As previously defined [1], *state* distinguishes the conditions or levels of being aware of anything at all from that being completely oblivious such as in general anesthesia or coma. *Contents* of consciousness refers to what one is aware of at a particular moment vs. what is outside of immediate awareness. Our central hypothesis is that state and contents are linked by a cooperation between the anterior forebrain mesocircuit and macroscale cortical networks, and that this cooperation is controlled by a few key brain areas (Fig. 1). To investigate, we will combine pharmacologic, psychologic and noninvasive brain stimulation approaches. We will alter the state of consciousness by propofol in healthy volunteers, and assess the contents of consciousness by applying a near-threshold perceptual task with Signal Detection Theory (SDT) metrics. Task-related brain activity will be assessed by simultaneous fMRI. We will also apply transcranial low-intensity focused ultrasound pulsation (LIFUP) to stimulate specific brain regions and assess their causal involvement in the control of conscious state and contents. From a basic science perspective, this work will help understand the neural basis of consciousness, which is one of the most fundamental unsolved problems of neuroscience. From a clinical perspective, the work will facilitate better understanding of the neural mechanism of the anesthetics' sedative-hypnotic effects, which is a prerequisite for future enhancements of clinical anesthesiology.

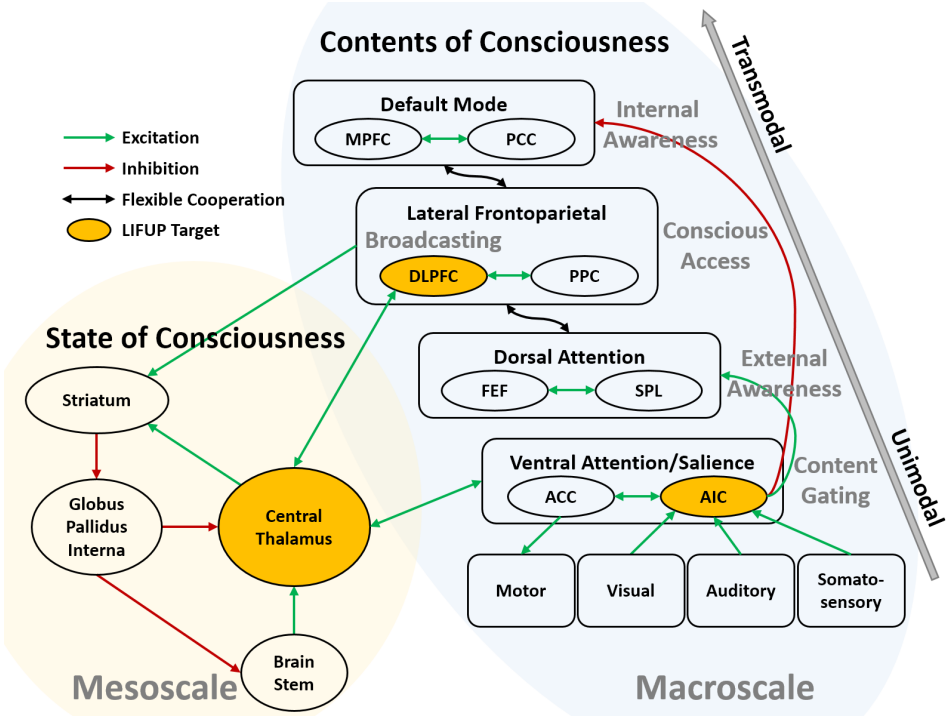

Fig. 1. *Schematic illustration of the central hypothesis. The state and contents of consciousness are linked by a cooperation between the anterior forebrain mesocircuit and the macroscale cortical networks, controlled by a few key brain areas. The central thalamus (CT) controls the state of consciousness. The anterior insula cortex (AIC) gates conscious contents and regulates brain network switches between dorsal attention (associated with external awareness) and default mode (associated with internal awareness)*

networks. The dorsolateral prefrontal cortex (DLPFC) within the lateral frontoparietal network has a flexible cooperation with the dorsal attention and default mode networks, and it initiates brain-wide global broadcasting of contents that leads to reportable conscious experience known as access consciousness. Macroscale brain networks unfold along a hierarchical cortical organization from unimodal to transmodal regions. The CT, AIC and DLPFC are target areas with LIFUP. Abbreviations: medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), posterior parietal cortex (PPC), frontal eye field (FEF), superior parietal lobe (SPL), anterior cingulate cortex (ACC).

Rationale and Hypothesis

Investigations into the state and contents of consciousness have traditionally progressed independently. However, we previously proposed that the state and contents of consciousness are fundamentally linked, and they can be neither studied nor understood in isolation from each other [2]. Thus, a gap of knowledge exists, mainly due to the lack of systematic investigations into both aspects of consciousness with the same experimental setup. The research proposed here is designed to overcome this gap by discovering the neural linkages between state and contents of consciousness. Our general hypothesis is that the relationship between state and contents of consciousness rests on the functional interaction of brain systems between meso- and macroscales. At mesoscale, the "anterior forebrain mesocircuit" hypothesis [3–5] encapsulates the role of central thalamic (CT) neurons and their frontostriatal connections in determining the *state* of consciousness. The mesocircuit also incorporates acceding projections from brainstem arousal nuclei and cooperates with the frontoparietal cortical network to generate conscious experience [5]. At macroscale, the *contents* of consciousness are thought to be determined through a hierarchical cortical organization along a cortical gradient from unimodal to transmodal areas [6]. Prior studies suggest the involvement of specific brain regions; particularly that of the AIC which gates conscious access of sensory information [7] by controlling the balance of activity between the default-mode and dorsal attention networks that correspond to internal and external awareness, respectively [8,9]. In addition, the DLPFC is thought to initiate brain-wide global broadcasting of contents to generate reportable conscious experience known as access consciousness [10–12].

In this study, we aim to determine how conscious contents are degraded during anesthetic modification of the conscious state, and to disentangle the causal roles of specific brain areas in state-content interaction through a perturbational approach. We hypothesize that suppressing the state of consciousness will diminish the quality of conscious contents and that this will be associated with functional alterations in three key brain areas: CT, AIC and DLPFC. We also hypothesize that stimulating the three areas will lead to differential perceptual outcomes (e.g., a change in subjective perceptual criterion alone, detection sensitivity alone, or both).

To test the hypotheses, we will (1) administer propofol to reduce the state of consciousness (moderate sedation), (2) perform near-threshold perceptual task to assess the contents of consciousness, (3) apply transcranial low-intensity focused ultrasound pulsation (LIFUP) to noninvasively stimulate the CT, AIC and DLPFC, and (4) perform functional magnetic resonance imaging (fMRI) to measure the related brain process during baseline, sedation, and sedation+LIFUP. We will measure the quality of conscious contents by two orthogonal quantities, criterion (c) and sensitivity (d') derived from the Signal Detection Theory. Here c captures the tendency of a subject to report subjective recognition of a target stimulus regardless of whether the target is present or absent, whereas d' captures the ability of a subject to distinguish between target present and absent trials.

We anticipate that suppressing the conscious state will decrease both c and d', indicating more conservative responses and reduced stimulus differentiation, while c and d' are differentially affected by the activity of DLPFC and AIC. Furthermore, neither c nor d' alone but their product will be associated with the activity of the CT, thus implying a putative mechanism for state-content

relationship by the functional interaction of brain areas CT for controlling state, and AIC and DLPFC for gating and broadcasting, respectively, the conscious contents. We also anticipate that stimulating the DLPFC and AIC will differentially change c and d'. Stimulating the CT will positively shift c and substantially increase d', thereby restoring perceptual performance to the awake baseline level. This will be associated with an increase of task-related activity in the DLPFC and AIC. If so, this would disentangle the causal roles of CT, AIC and DLPFC on perceptual outcomes.

Number of Subjects, Recruitment and Informed Consent

Statistical power analysis (see below) requires a group of 25 subjects. We plan to enroll 100 evaluable subjects randomly assign into four groups; we intend to enroll 150 subjects to account for unevaluable participants. See experimental design details below. Healthy participants will be recruited by listing on UMClinicalStudies.org and by postings at area colleges and community groups in Ann Arbor. Interested volunteers will call the phone number of a designated recruiter for an initial phone screening. The initial phone screening will consist of questionnaires related to medical history, demographic information, handedness, inclusion and exclusion criteria and procedure standard MRI screening questionnaire. If interested, the participant will complete the questionnaires, which will be reviewed by the study team. The health status will be confirmed by the attending anesthesiologist before the study on site. Once eligibility is confirmed by the study team, the one-time research study session will be scheduled. Participants will screened for COVID-19 prior to entry into the hospital per hospital guidelines. A standard face mask will be provided upon hospital entry if participants do not have one.

All participants will give written informed consent according to institutional guidelines prior to any testing. The Principal Investigators or their designee will obtain consent using a written consent form approved by the Institutional Review Boards of the University of Michigan Medical School (IRBMED). It will contain detailed information regarding the purpose, risks and benefits of participating. Copies of the signed consent form will be given to the subjects; the original consent will remain with the study team. Subjects will be compensated for their involvement.

Inclusion and Exclusion Criteria

Volunteers are screened using a medical history and demographics questionnaire.

Inclusion criteria*.* The subject population will consist of healthy study subjects with ASA-1 status. The participants' health status will be assessed by the attending anesthesiologist prior to inclusion in the study. The participants will be right-handed adults between the ages of 18 and 40 with a body mass index (BMI) less than 30. All subjects will be English speakers.

Exclusion criteria. Participants will be excluded if they have any medical contraindication to MRI scanning; are unable to undergo MRI scanning because of possible pregnancy or currently breastfeeding, BMI>30, metallic substances in the body, claustrophobia, anxiety, or cardiopulmonary disease; or have an intracranial structural abnormality on T1-weighted MRI scans. Potential subjects will be excluded if they have a history of allergy to propofol, eggs or egg products, soybean or soybean products, neurological, cardiovascular, or pulmonary illness; significant head injury with loss of consciousness; learning disability or other developmental disorder; sleep apnea or any severe snoring history; gastroesophageal reflux disease (GERD) or heartburn; pancreatitis or a history of pancreatitis, or sensory/motor loss sufficient to interfere with performance of the study. Participants with tattoos in the head or neck region will be excluded from study; other tattoos are subject to determination by investigators based on their assessment regarding participant safety. To eliminate aspiration risk subjects will also be excluded if they have had recent food or liquid intake (within 8 hours). Subjects will be excluded if they have a history of drug use, have a positive drug screen, are unwilling to abstain from alcohol for 24 hours prior to dosing, or have a current history of nicotine use. Women will be required to take a pregnancy

test prior to participation to ensure a negative result. The pre-scan drug screen and pregnancy test will be paid for by the study.

Participants will be compensated $200 for completing the one-time fMRI scanning visit. Participants who have shaved or no hair, or those willing to shave the left side of their temple will be compensated an additional $75.

Methods and Procedures

Imaging

Noninvasive functional magnetic resonance imaging will be performed in the Philips 3T (MR2) Research MRI (standard 32-channel transmit/receive head coil) at the University of Michigan Health System, University Hospital, Department of Radiology.

1) SPGR high-resolution images. T1 weighted spoiled gradient recalled echo (SPGR) images will be acquired for high spatial resolution of anatomical images with parameters: 170 sagittal slices, 1.0mm thickness (no gap), TR=8.1s, TE=3.7ms, flip angle=8°, FOV=24cm, image matrix 256×256.

2) Functional MRI images. A gradient-echo EPI pulse sequence will be employed to acquire functional images over the whole brain with parameters: 28 slices, TR/TE=800/25ms (multiband fMRI acquisition), slice thickness=4mm, in-plane resolution=3.4×3.4mm; MB factor=4; field of view (FOV)=220mm, flip angle=76°, image matrix: 64×64. The imaging protocols and data acquisition will be completed within 2.5 hours scanning session for each subject.

Anesthesia

Anesthetic agents. In both experiments, propofol will be applied because it has been the most widely-used agent in human fMRI studies of anesthetic effects in brain activity [13–16] and we have considerable experience in this field [7,17–21]. The advantage of propofol is that it exerts minimal effects on cerebral and systemic hemodynamics [22,23] and therefore does not confound the fMRI results. Propofol suppresses neuronal activity mainly through an enhancement of GABA-A receptor-mediated inhibition thus modulating widespread targets across the brain.

Anesthetic administration and monitoring. Both experiments will be performed by the attending anesthesiologists. Sedation will be achieved by target-controlled IV infusion of propofol. The IV line will be placed after application of a local anesthetic. Nasal cannula will be used for supplemental O_2 and CO_2 sampling. Spontaneous respiration, end-tidal CO_2, heart rate, and electrocardiogram will be continuously monitored during the experiment. Noninvasive arterial pressure will be measured with magnetic resonance (MR)-compatible automatic monitor. Post anesthesia care will consist of checking vital signs for 1 hour by the nursing staff. A wheelchair will be provided to assist the participant if needed. All anesthesia equipment, supplies, and drugs will be provided by anesthesiologists from the University of Michigan Health System.

LIFUP Method

We will utilize the BrainSonix BXPulsar 1002 LIFUP System (BrainSonix Inc. http://www.brainsonix.com/). FDA has determined that our proposed clinical investigation is a nonsignificant risk (NSR) device study because it does not meet the definition of a significant risk (SR) device under 21 CFR 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812). An IDE application is not required to be submitted to, or approved by, FDA for a NSR study. This device contains a single-element, air-backed, spherical section ultrasound transducer with 61 mm diameter and 80 mm focal depth. The transducer is mounted in a plastic housing filled

with deionized, de-gassed water and sealed with a thin polyethylene membrane permeable to ultrasound. The transducer will be coupled to the scalp of the participant using a 3D-printed transducer holder that allows for sonication to occur in conjunction with ultrasonic standoff pads and ultrasound gel. The LIFUP system operates at a fundamental frequency of 650 kHz. Following the previous work [24,25], we plan to administer a pulse repetition frequency of 100 Hz and pulse width of 0.5 ms. A total of 30 sonications will be administered, with a derated spatial-peak temporal-average intensity (Ispta) of 720 mW/cm^2, each lasting 30 s, separated by 30 s pause intervals. Sonication will be administered in a 3 Tesla Philips scanner at University of Michigan Hospital. Using a rapid structural MRI sequence, the perpendicular will be adjusted along the apex of the transducer's concavity directly targeting a region of interest. We will utilize a neuronavigation system (Brainsight Navigation system, Brainbox Ltd, https://brainbox-neuro.com/products/brainsight-tms-navigation) to ensure precise targeting and positioning of the transducer. At the target location, the estimated peak pressure will be 0.71 MPa, and the ultrasound beam width will be 5 mm. The estimated targeting accuracy (uncertainty) at the desired location is ±2.5 mm.

Experimental Design

Three 30-min sessions will be conducted including wakeful baseline, moderate sedation, and the application of LIFUP under moderate sedation (sedation+LIFUP) with an effect-site concentrations of 1.5 µg/ml (Fig. 2). Moderate sedation will be achieved by IV infusion of propofol to achieve effect-site concentrations of 1.5 µg/ml. Infusion rate will be manually controlled. An initial bolus dose and subsequent infusion rate for each participant will be pre-determined based on a pharmacokinetic model [26] developed for target-controlled propofol infusion and implemented in software (STANPUMP [27]). A 5-min equilibration period between baseline and moderate sedation will be included. After sedation+LIFUP session, the infusion will be terminated allowing for spontaneous recovery of consciousness. A random group assignment will be applied in four groups of participants receiving LIFUP with sham control, or in the DLPFC, AIC, or CT, respectively.

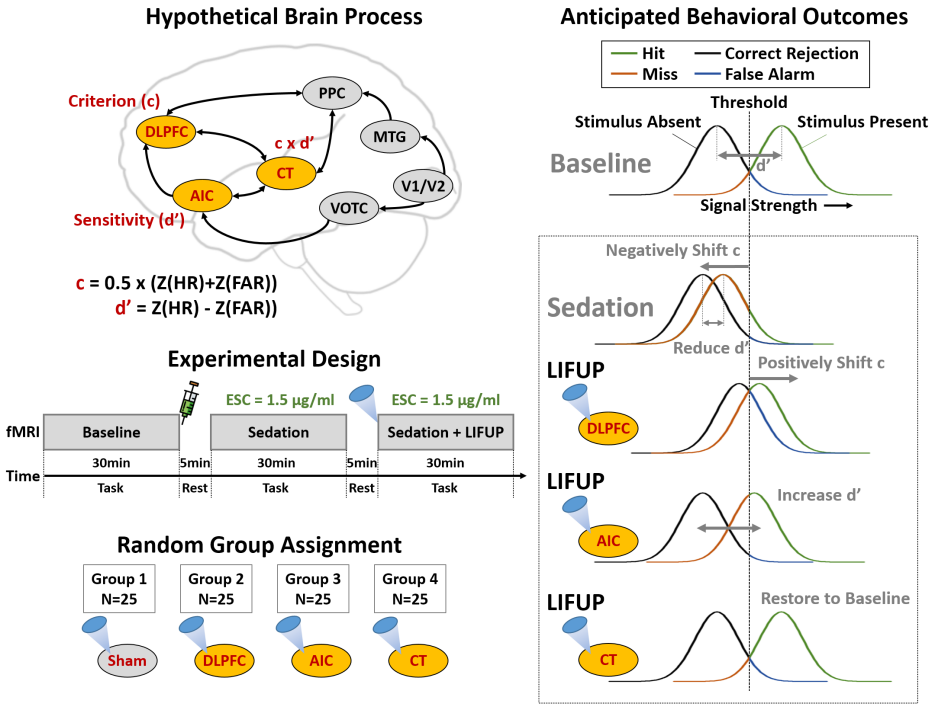

Fig. 2. *Concept, design and anticipated outcomes. In the hypothetical brain process (top left) visual*

information propagates through ventral (V1/V2-->VOTC) and dorsal (V1/V2-->MTG-->PPC) pathways. The AIC receives inputs from the VOTC and prioritizes the inputs before sending them to the DLPFC for global broadcasting. The activities of DLPFC and AIC are hypothetically associated with two orthogonal SDT quantities, criterion (c) and sensitivity (d'). Given the wiring of the mesocircuit and thalamocortical loops (e.g., DLPFC-CT, and AIC-CT), the CT is hypothetically associated with the product of c and d'. Experimental design (bottom left) includes three fMRI sessions: wakeful baseline, moderate sedation, and LIFUP under moderate sedation. Participants will be assigned at random to four groups: those receiving LIFUP to DLPFC, AIC, CT or sham control. Anticipated effects are illustrated (right). Abbreviations: early visual cortex (V1/V2), ventral occipitotemporal cortex (VOTC), middle temporal gyrus (MTG), posterior parietal cortex (PCC).

Visual task. Participants will be asked to lay in the scanner, pay attention on the screen, and complete an image recognition task. All stimuli will be programmed using E-Prime (Psychology Software Tools, Pittsburgh, PA) and delivered via a visual presentation system designed for an MRI environment. Stimuli will be presented at the threshold of subjective recognition. An adaptive thresholding procedure will be conducted whereby image contrast will be titrated to reach a 50% subjective recognition rate for each subject. Stimuli will include two common visual object categories: faces and houses. Participants' task is to report the category ("F" or "H") of an image presented and their recognition experience ("Yes" or "No") (Fig. 3). Specifically, they will be instructed to report the object category regardless of their recognition experience and, in cases of unrecognized images, to make a genuine guess (two-alternative choice discrimination). Then, they will be instructed to report whether they see an object, such that even if the object appears unclear or noisy, they should respond "yes", but if they see nothing or only low-level features, such as cloud-like abstract patterns, they should respond "no".

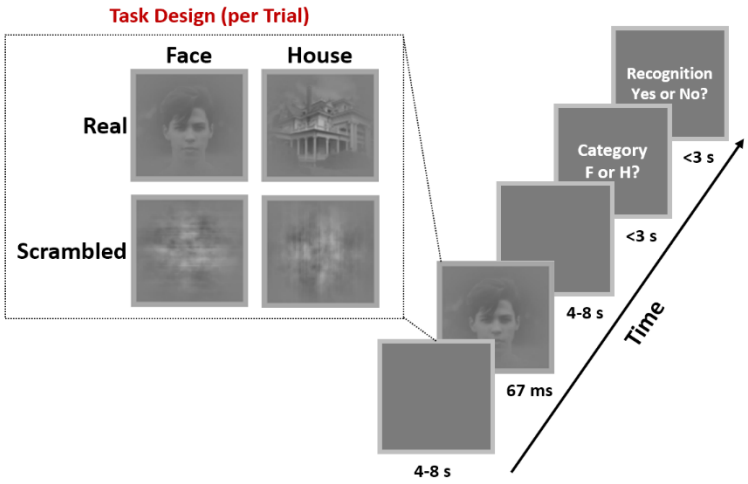

Fig. 3. *Visual task design. During each 30-min session, participants will complete an image recognition task. Stimuli (faces, houses, and scrambled images) will be presented at the threshold of subjective recognition. Participants' task is to report the category ("F" or "H") of the image presented and their recognition experience ("Yes" or "No").*

The stimulus set will include real and scrambled images, where the scrambled images will be created by phase-shuffling a randomly chosen real image from each category to preserve category specific low-level image features [28]. Because scrambled images do not include an object stimulus, they are used as "catch trials" to determine the subjects' baseline tendency to give positive responses to a question about their recognition experience. Each object category will include four unique real images and one scrambled image. Each image will be repeated 10 times (i.e., trials) for each 30-min session. The pre-stimulus interval will vary randomly from trial to trial between 4 and 8 seconds to prevent stimulus timing predictability. The stimuli will be presented in a randomized order to prevent category predictability.

Primary Outcome Measure: Blood Oxygen Level Dependent (BOLD) response to visual stimuli (timeframe: baseline to 90 minutes).

Secondary Outcome Measure: Perceptual criterion (c) and sensitivity (d') derived from the Signal Detection Theory (SDT) (timeframe: baseline to 90 minutes).

Data Analysis and Statistics

For each 30-min session, we will calculate SDT metrics of sensitivity (d') and criterion (c) using subjective reports of recognition as "yes" or "no". The d' indicates the ability to discriminate between real and scrambled images. It is computed by subtracting the z-transformed False Alarms Rate (FAR) from the z-transformed Hit Rate (HR): d' = Z(HR) - Z(FAR)), where Z is an inverse normal cumulative distribution function. The c represents the tendency to make "yes" reports to indicate recognition, regardless of whether the stimulus is a real or a scrambled image, which is computed as: c = 0.5 x (Z(HR)+Z(FAR)). We will also calculate percent of correct responses as an operational measure of two alternative-forced-choice sensitivity using subjective category reports, i.e., responses to the first question: "Face" or "House".

For fMRI data, preprocessing steps will be implemented in AFNI (http://afni.nimh.nih.gov/afni). 1) Slice timing correction; 2) Rigid head motion correction/realignment within and across runs; frame-wise displacement (FD) of head motion was calculated using frame-wise Euclidean Norm (square root of the sum squares) of the six-dimension motion derivatives. A frame and its each previous frame will be tagged as zeros (ones, otherwise) if the given frame's derivative value has a Euclidean Norm above FD=0.5 mm; 3) Coregistration with high-resolution anatomical images; 4) Spatial normalization into Talairach stereotactic space and resampling to $3 \times 3 \times 3$ mm^3; 5) using AFNI's function 3dTproject, the time-censored data will be high-pass filtered above 0.008 Hz. Undesired components (e.g., physiological estimates, motion parameters) will be removed via linear regression. The latter include linear and nonlinear drift, time series of head motion, its temporal derivative, and mean time series from the white matter and cerebrospinal fluid; 6) Spatial smoothing with 6 mm full-width at half-maximum isotropic Gaussian kernel; 7) The time-course per voxel of each run will be normalized to zero mean and unit variance, accounting for differences in variance of non-neural origin (e.g., distance from head coil).

We will calculate the average BOLD activity (across the trials with real images) in the regions of interest including the CT, AIC, and DLPFC. For a given measurement, repeated-measures ANOVA plus post-hoc tests will be performed at the group level. Inter-subject multivariate linear regression analyses will be performed with SDT metrics as dependent variables and average BOLD activity as independent variables. Statistical significance will be defined at FDR-corrected $\alpha < 0.05$.

Anticipated Results and Interpretation

We expect to observe a decrease of both c and d' during sedation, indicating more conservative responses and reduced stimulus differentiation. This would suggest that suppressing the state of consciousness diminishes the quality of conscious content. We also expect to find an overall reduction of average BOLD activity across all examined regions, i.e., in CT (state control), AIC (content gating) and DLPFC (content broadcasting). Furthermore, the change of c (baseline vs. sedation) may be associated with the change of DLPFC's average BOLD activity, and the change of d' may be associated with the change of AIC's average BOLD activity. The change of c × d' may be associated with the change of CT's average BOLD activity. Because the activity of CT supervenes on the activity of DLPFC and AIC, the state (CT) and contents (DLPFC/AIC) are altered together in sedation. If found, the results would suggest a neural mechanism for the linkage between state and contents. We also anticipate that the LIFUP stimulation in DLPFC during sedation will increase c without changing d' and increase the average BOLD activity in the

DLPFC. Stimulation of the AIC will increase d' without changing c, possibly through an enhancement of salience/attentional process offsetting the general inhibitory effect of propofol. Importantly, stimulation of the CT is expected to substantially increase both d' and c, arguably restoring perceptual performance to baseline level. This may be accompanied by an overall increase of average BOLD activity along the entire visual processing pathway.

Power Analysis

For an fMRI study of cognitive function, Desmond and Glover [29] reported that about 25 subjects are necessary to achieve 80% power for a 0.5% increase of activity. We also conducted power analysis based on our previous study with graded sedation of propofol [30]. The average Cohen's d as a measure of the effect size was 0.56. For 80% power and α=0.05, N=24 human subjects will be needed. The obtained subject number is also very close to the suggested optimal group size for reliable statistics in functional MRI studies [31]. We plan for a minimum of 25 subjects per group.

Biological Variables

We will recruit participants of both sexes with various ethnic/racial backgrounds, aiming for diversity and equal representation. The age range will be limited to 18-40 years in order to limit age-dependent variation in anesthetic requirement for sedation and for participant safety.

Human Studies and Safety Profile related to LIFUP

The first human application of the LIFUP technique targeted the primary somatosensory cortex of healthy volunteers in a sham-controlled study [32]. Subsequently, low-intensity ultrasonic thalamic stimulation was successfully applied to facilitate the emergence of a patient from minimally conscious state after acute brain injury [25]. This was followed up by the recent report on the same subject [24] and ongoing clinical trial for thalamic low-intensity focused ultrasound modulation of consciousness following in brain injury (Nct02522429; https://clinicaltrials.gov/ct2/show/NCT02522429).

LIFUP has important advantages over formerly applied interventions that makes it a highly promising clinical tool. Compared to existing magnetic or electric noninvasive brain stimulation, LIFUP provides superior spatial resolution on the millimeter scale as well as the capability to target sub-cortical structures non-invasively. Because of LIFUP' high spatial resolution and ability to stimulate at depth, it is also of particular interest to pair with concurrent magnetic resonance imaging (MRI) that helps both precise targeting and readout of the stimulation effects.

The biophysical mechanism of LIFUP is not fully understood; several mechanisms including mechanically induced changes in membrane capacitance, cavitation events, and mechanical sensitivity of voltage-gated ion channels [33,34] have been proposed. Currently, the ion channel modulation theory seems to be most plausible [33,35]. Although a few studies reported inhibitory effects of LIFUP on visual-evoked potentials in animals [36,37] and somatosensory-evoked potentials in humans [32], the majority of LIFUP studies have reported motor or sensory effects consistent with neural excitation (a recent review by [38]).

The application of LIFUP over 0.5–5 min has been shown to produce persistent neuromodulatory effects, lasting from a few minutes to several hours. For example, excitation-like effects and changes in functional connectivity lasting for over an hour were reported in nonhuman primates and human subjects. Stimulation of the amygdala and supplementary motor area in nonhuman primates affected circuit connectivity, resulting in a change in coupling of fMRI activity between the LIFUP target and other brain areas [39,40]. LIFUP stimulation of the frontal eye field of macaques for 100 ms immediately before a visual cue shifted the bias of a choice task in favor of

the corresponding contralateral side [41]. The forgoing evidence supports the feasibility and potential effectiveness of LIFUP to modulate circuitry of interest.

LIFUP has been shown to be a safe and effective method to modulate human brain activity, when the stimulation parameters and protocol follow the available guidelines [38,42,43]. The majority of studies with ultrasound have reported no adverse events or evidence of anatomical damage [32,44–47]. Mild and moderate symptoms were reported such as neck pain, sleepiness, muscle twitches, itchiness, and headache [48,49]. An in-depth survey of the safety of ultrasound for human neuromodulation did not find any evidence of serious events in a large cohort of participants [50]. Specifically, 64/120 participants (53%) responded to follow-up questionnaire, and none of them experienced serious adverse effects. 7/64 reported mild to moderate symptoms (e.g., neck pain, problems with attention, muscle twitches and anxiety), that were perceived as 'possibly' or 'probably' related to participation in LIFUP experiments. The most common unrelated symptoms included sleepiness and neck pain. There were initial transient reports of mild neck pain, scalp tingling and headache that were extinguished upon follow-up. No new symptoms were reported upon follow up out to 1 month [50]. In addition, no studies have shown LIFUP induced tissue damage in the absence of heating, unless they utilized contrast agents to enhance cavitation effects [34]. Finally, the LIFUP appears to be safe even at intensities several times higher than the FDA limit for diagnostic ultrasound (720 mW/cm^2) [51].

Potential Risks related to MRI Scanning

There are no known risks associated with magnetic resonance imaging, as long as technical parameters remain within FDA guidelines. A licensed MR technologist is instructed in these guidelines and performs all machine manipulations. Complete histories, physical examinations and stringent medical guidelines exclude many potential subjects before they enter the study, thereby further minimizing risks. A crash cart is always present and regular safety drills are performed by the medical and experimental staff to prepare for any untoward effects.

MRI Static Magnetic Fields: FDA guidelines for clinical product scanners limit the main magnetic field to 3 Tesla. Our studies will be performed on a standard, clinical 3 T Philips scanner. A substantial body of literature exits that supports the safety of field strengths up to 7 T. There are no known risks of exposure to 3 or 7 T fields for MR imaging.

Among the reported biological effects of exposure to strong static magnetic fields are the following: 1) Dizziness (with nausea) or stimulation of the sensory nerves in the soft palate has been reported as a result of the subject's head being moved while in the magnet. 2) Rapid eye movement has been reported (at 4 and 7 T) to cause magnetophosphene effects. First described in 1896, these flickering light sensations are similar to visual phenomena caused by direct electric current passage across the head or retina.

Radiofrequency (rf) Magnetic Fields: Radiofrequency energy burns are the result of high electric fluxes in the immediate vicinity of the patient. All MRI systems create some rf electric fields incidental to the production of the intended rf magnetic fields. The potential causes are malfunctions in the rf coil switching circuitry, improper use of the surface coils, design flaws in some clinical MRI system surface coils or cardiac gating patient connection leads. Nationally, 60 burn incidents have been reported to the FDA in the course of approximately 11 million exams. Our site has never experienced any difficulty in this regard.

Acoustic Noise: The sound generated by an MR system usually consists of a series of repetitive pulses. The relevant safety parameters required to characterize such a noise are the peak impulse sound pressure level (Lpeak) and the time integral of the A-weighted sound pressure level (Leq). In MR applications, the peak impulse sound pressure level is dependent upon the peak amplitude of the individual pulses, while the time integral of the A-weighted sound pressure

level is dependent upon the continuous exposure to a series of such pulses. Acoustic noise is a result of the mechanical vibration produced by the gradient coils when the nominally large currents are applied to them to create time varying imaging gradient fields. The sound produced can be loud enough to produce temporary deafness (up to 95 dB). Foam earplugs will attenuate this noise by up to 30 dB. They are in routine use at the 3T systems, and have been proven effective.

Claustrophobia: While inside the magnet, subjects may experience an acute panic attack due to claustrophobia. Subjects are all prescreened for fear of tight places. Once inside the magnet, the subject will be given a squeeze ball to signal the MR operator if he or she is under acute distress.

Potential Risks related to Anesthesia

Risks associated with intravenous catheter placement include brief, local discomfort and possible bruising, which can occur at the site of the IV line. There is also a possible (rare) chance of infection, but every precaution will be taken to reduce this risk by keeping the IV site clean and dry. Risks associated with propofol administration include: pain at the site of injection, possible allergic reaction to the drug, depression of respiration which may necessitate placement of an endotracheal tube to assist breathing, and mechanical ventilation, or a decrease in blood pressure which may necessitate giving a drug or IV fluids to bring the subject's blood pressure up. These effects disappear when propofol is discontinued.

Justification for the Risks Involved

The risks of the proposed procedure are minimal, and the importance to mankind of the potential knowledge gains is substantial, making the risk/benefit ratio very low. We combine the state-of-the-art brain imaging facility currently in place in the University of Michigan Health System with the experience of the imaging staff and clinic anesthesiologists in the Department of Anesthesiology. These experiments will provide a unique opportunity to understand the neurophysiological mechanisms of anesthesia modulation of human consciousness. Therefore, we will provide a unique opportunity to expand our knowledge of anesthesia-modulated human consciousness.

Procedures for Minimizing Risks

All research subjects will go through a screening process for inclusion and exclusion criteria performed by licensed physician. A licensed physician will be present at all MRI scanning sessions to monitor the subjects. When subjects express or exhibit anxiety regarding the scanner setting, they will be allowed to discuss these feelings. Attempts will be made to minimize the discomfort and anxiety. When in the scanner, subjects will be provided with a squeeze-ball alarm that will alert the scanner technician and the researcher that the subject desires to come out of the scanner. In such instances, the subject will immediately be removed from the scanner and appropriate measures will be taken to ensure his or her psychological health. Earplugs, demonstrated to reduce scanner noise to a non-damaging level, will be used to minimize hearing risks.

In addition, any other health problem that would be aggravated by an MRI scan will also be a cause for terminating the subject’s participation. In the event of serious cardiac-respiratory problems or other medical emergencies, the hospital code team will be activated. Other medical problems will be treated by the monitoring physician. Any medical problems that arise after release, although unlikely, will be treated by a physician from the research team. All subjects will have to arrange transportation after the study, and agree to not drive, work, operate machinery, or make legal decisions for 24 hours after the study. Subjects will be informed of their right to withdraw from the study at any time.

A protocol has been established to handle unexpected medical emergencies arising in the scanner suite. This protocol deals with medical issues and the duties of each team member. This includes stopping the scanner, removing the patient and calling for outside medical assistance. All members of the research team participate in periodic emergency protocol drills in the scanner suite and a copy of the written protocol and protocol termination guidelines are present at all times. Subjects requiring intervention for any neurological or cardiovascular adverse event will be transferred to the Emergency Department for further evaluation and treatment as seen fit by the attending physician. More serious cardiac events such as ventricular tachycardia, ventricular fibrillation or any unstable rhythm will be immediately treated according to current Advanced Cardiovascular Life Support (ACLS) protocols. Research team physicians have immediate access to valium, diphenhydramine, epinephrine, lidocaine, and NTG for emergency use, in addition to a fully supplied and operational "crash cart" with EKG, defibrillator, suction, oxygen, and airway management equipment.

We plan to keep the LIFUP's intensity strictly under the FDA limit for diagnostic ultrasound (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/marketing-clearance-diagnostic-ultrasound-systems-and-transducers). We will also perform a few pilot experiments to evaluate possible mild and moderate symptoms without the administration of propofol anesthetic.

Adverse Events

Adverse events will be monitored throughout the procedures and for 24 hours after the procedure via a phone call to the subjects. We will follow their medical record for 30 days following the procedure. Complications or adverse events that are observed by the investigator or reported by the subject will be recorded. For all adverse events and complications, a description of the event, date first observed, any action taken and ultimate outcome will be recorded.

For all adverse events, sufficient information will be pursued and/or obtained as to permit 1) an adequate determination of the outcome of the event (i.e. whether the event should be classified as a serious adverse event) and; 2) an assessment of the causal relationship between the adverse event and the investigational device, or if applicable, the other study treatments of diagnostic product(s). Adverse events felt to be associated with the investigational device, or if applicable, other study treatment or diagnostic product(s) will be followed until the event (or it sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the sponsor-investigator. Adverse events will be reported to the IRB according to their reporting guidelines.

Serious and Unanticipated Adverse Device Events

An unanticipated adverse device event is defined as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

The sponsor-investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the investigational device or, if applicable, other study treatment of diagnostic products(s) and 3) if the adverse event meets the criteria for a serious adverse event. The sponsor shall promptly report the results of an evaluation of any serious and unanticipated adverse event to the FDA, the University of Michigan IRBMED and participating investigators (if any) as soon as possible, but not later than 10 working days after the sponsor first receives notice of the effect.

Confidentiality

Strict subject confidentiality will be maintained. Subjects will be assigned a code number following their first contact in the protocol. This number will be used throughout the experiment and will be the only identifier on behavioral and physiological archival data, and magnetic resonance (MR) scans. The identity of subjects will not be revealed at scientific meetings, in publications or other vehicles of public communication. Data will be pooled across subjects where appropriate. Only the PIs, Co-investigators, and the study coordinator will have access to the ID code, which will be stored in a locked file separate from the data.

Any behavioral data collected on the subjects will be coded by study ID numbers and entered directly into notebook computers used in the field. These computers are password protected and stored behind a locked door when not in use. Clinical and biographic data are entered into the database using the ID number only. Only select staff members have access to the actual paper copies. Medical information will be released by name only to health care providers, and then only with written permission from the subject.

References

1. Laureys S. The neural correlate of (un)awareness: Lessons from the vegetative state. Trends Cogn Sci. 2005;9: 556–559. doi:10.1016/j.tics.2005.10.010
2. Bachmann T, Hudetz AG. It is time to combine the two main traditions in the research on the neural correlates of consciousness: C=LxD. Front Psychol. 2014;5: 1–13. doi:10.3389/fpsyg.2014.00940
3. Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis [Internet]. Trends in Neurosciences. Trends Neurosci; 2010. pp. 1–9. doi:10.1016/j.tins.2009.11.002
4. Edlow BL, Claassen J, Schiff ND, Greer DM. Recovery from disorders of consciousness: mechanisms, prognosis and emerging therapies [Internet]. Nature Reviews Neurology. Nature Research; 2021. pp. 135–156. doi:10.1038/s41582-020-00428-x
5. Laureys S, Schiff ND. Coma and consciousness: Paradigms (re)framed by neuroimaging. Neuroimage. 2012;61: 478–491. doi:10.1016/j.neuroimage.2011.12.041
6. Margulies DS, Ghosh SS, Goulas A, Falkiewicz M, Huntenburg JM, Langs G, et al. Situating the default-mode network along a principal gradient of macroscale cortical organization. Proc Natl Acad Sci U S A. 2016;113: 12574–12579. doi:10.1073/pnas.1608282113
7. Huang Z, Tarnal V, Vlisides PE, Janke EL, McKinney AM, Picton P, et al. Anterior insula regulates brain network transitions that gate conscious access. Cell Rep. Elsevier B.V.; 2021;35. doi:10.1016/j.celrep.2021.109081
8. Demertzi A, Soddu A, Laureys S. Consciousness supporting networks. Curr Opin Neurobiol. 2013;23: 239–244. doi:10.1016/j.conb.2012.12.003
9. Huang Z, Zhang J, Wu J, Mashour GA, Hudetz AG. Temporal circuit of macroscale dynamic brain activity supports human consciousness. Sci Adv. American Association for the Advancement of Science; 2020;6: 1–14. doi:10.1126/sciadv.aaz0087
10. Dehaene S, Changeux J-PP. Experimental and Theoretical Approaches to Conscious Processing. Neuron. Elsevier Inc.; 2011;70: 200–227. doi:10.1016/j.neuron.2011.03.018
11. Mashour GA, Roelfsema P, Changeux JP, Dehaene S. Conscious Processing and the Global Neuronal Workspace Hypothesis. Neuron. Elsevier Inc.; 2020;105: 776–798.

doi:10.1016/j.neuron.2020.01.026

12. Van Vugt B, Dagnino B, Vartak D, Safaai H, Panzeri S, Dehaene S, et al. The threshold for conscious report: Signal loss and response bias in visual and frontal cortex. Science (80-). 2018;360: 537–542. doi:10.1126/science.aar7186

13. Boveroux P, Vanhaudenhuyse A, Bruno M-AA, Noirhomme Q, Lauwick S, Luxen A, et al. Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. Anesthesiology. 2010;113: 1038–53. doi:10.1097/ALN.0b013e3181f697f5

14. Guldenmund P, Demertzi A, Boveroux P, Boly M, Vanhaudenhuyse A, Bruno M-A, et al. Thalamus, brainstem and salience network connectivity changes during propofol-induced sedation and unconsciousness. Brain Connect. 2013;3: 273–85. doi:10.1089/brain.2012.0117

15. Schroter MS, Spoormaker VI, Schorer A, Wohlschlager A, Czisch M, Kochs EF, et al. Spatiotemporal Reconfiguration of Large-Scale Brain Functional Networks during Propofol-Induced Loss of Consciousness. J Neurosci. 2012;32: 12832–12840. doi:10.1523/jneurosci.6046-11.2012

16. Schrouff J, Perlbarg V, Boly M, Marrelec G, Boveroux P, Vanhaudenhuyse A, et al. Brain functional integration decreases during propofol-induced loss of consciousness. Neuroimage. 2011;57: 198–205. doi:10.1016/j.neuroimage.2011.04.020

17. Liu X, Lauer KK, Ward BD, Li SJ, Hudetz AG. Differential effects of deep sedation with propofol on the specific and nonspecific thalamocortical systems: A functional magnetic resonance imaging study. Anesthesiology. 2013;118: 59–69. doi:10.1097/ALN.0b013e318277a801

18. Huang Z, Wang Z, Zhang JJ, Dai R, Wu J, Li Y, et al. Altered temporal variance and neural synchronization of spontaneous brain activity in anesthesia. Hum Brain Mapp. 2014;35: 5368–5378. doi:10.1002/hbm.22556

19. Huang Z, Zhang JJ, Wu J, Qin P, Wu X, Wang Z, et al. Decoupled temporal variability and signal synchronization of spontaneous brain activity in loss of consciousness: An fMRI study in anesthesia. Neuroimage. 2016;124: 693–703. doi:10.1016/j.neuroimage.2015.08.062

20. Huang Z, Liu X, Mashour GA, Hudetz AG. Timescales of intrinsic BOLD signal dynamics and functional connectivity in pharmacologic and neuropathologic states of unconsciousness. J Neurosci. 2018;38: 2304–2317. doi:10.1523/JNEUROSCI.2545-17.2018

21. Huang Z, Vlisides PE, Tarnal VC, Janke EL, Keefe KM, Collins MM, et al. Brain imaging reveals covert consciousness during behavioral unresponsiveness induced by propofol. Sci Rep. 2018;8: 13195. doi:10.1038/s41598-018-31436-z

22. Kondo Y, Hirose N, Maeda T, Suzuki T, Yoshino A, Katayama Y. Changes in cerebral blood flow and oxygenation during induction of general anesthesia with sevoflurane versus propofol. Advances in Experimental Medicine and Biology. 2016. p. 479. doi:10.1007/978-1-4939-3023-4_60

23. Fiset P, Daloze T, Plourde G, Meuret P, Bonhomme V, Hajj-ali N, et al. Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study. J Neurosci. 1999;19: 5506–5513. Available: http://www.ncbi.nlm.nih.gov/pubmed/10377359

24. Cain JA, Spivak NM, Coetzee JP, Crone JS, Johnson MA, Lutkenhoff ES, et al. Ultrasonic Thalamic Stimulation in Chronic Disorders of Consciousness. Brain Stimul. Elsevier BV; 2021;14. doi:10.1016/j.brs.2021.01.008

25. Monti MM, Schnakers C, Korb AS, Bystritsky A, Vespa PM. Non-Invasive Ultrasonic Thalamic Stimulation in Disorders of Consciousness after Severe Brain Injury: A First-in-Man Report [Internet]. Brain Stimulation. Elsevier Inc.; 2016. pp. 940–941. doi:10.1016/j.brs.2016.07.008

26. Marsh B, White M, Morton N, Kenny GNC. Pharmacokinetic model driven infusion of propofol in children. Br J Anaesth. 1991;67: 41–48. doi:10.1093/bja/67.1.41

27. Shafer S. STANPUMP User's Manual. 1996;

28. Podvalny E, Flounders MW, King LE, Holroyd T, He BJ. A dual role of prestimulus spontaneous neural activity in visual object recognition. Nat Commun. Nature Publishing Group; 2019;10. doi:10.1038/s41467-019-11877-4

29. Desmond JE, Glover GH. Estimating sample size in functional MRI (fMRI) neuroimaging studies: Statistical power analyses. J Neurosci Methods. 2002;118: 115–128. doi:10.1016/S0165-0270(02)00121-8

30. Liu X, Lauer KK, Ward BD, Rao SM, Li SJ, Hudetz AG. Propofol disrupts functional interactions between sensory and high-order processing of auditory verbal memory. Hum Brain Mapp. 2012;33: 2487–2498. doi:10.1002/hbm.21385

31. Thirion B, Pinel P, Mériaux S, Roche A, Dehaene S, Poline JB. Analysis of a large fMRI cohort: Statistical and methodological issues for group analyses. Neuroimage. 2007;35: 105–120. doi:10.1016/j.neuroimage.2006.11.054

32. Legon W, Sato TF, Opitz A, Mueller J, Barbour A, Williams A, et al. Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans. Nat Neurosci. Nat Neurosci; 2014;17: 322–329. doi:10.1038/nn.3620

33. Tyler WJ. Noninvasive neuromodulation with ultrasound? A continuum mechanics hypothesis. Neuroscientist. Neuroscientist; 2011;17: 25–36. doi:10.1177/1073858409348066

34. Bystritsky A, Korb AS, Douglas PK, Cohen MS, Melega WP, Mulgaonkar AP, et al. A review of low-intensity focused ultrasound pulsation [Internet]. Brain Stimulation. Brain Stimul; 2011. pp. 125–136. doi:10.1016/j.brs.2011.03.007

35. Kubanek J, Shi J, Marsh J, Chen D, Deng C, Cui J. Ultrasound modulates ion channel currents. Sci Rep. Nature Publishing Group; 2016;6. doi:10.1038/srep24170

36. Yoo SS, Bystritsky A, Lee JH, Zhang Y, Fischer K, Min BK, et al. Focused ultrasound modulates region-specific brain activity. Neuroimage. Neuroimage; 2011;56: 1267–1275. doi:10.1016/j.neuroimage.2011.02.058

37. Kim H, Park MY, Lee SD, Lee W, Chiu A, Yoo SS. Suppression of EEG visual-evoked potentials in rats through neuromodulatory focused ultrasound. Neuroreport. Lippincott Williams and Wilkins; 2015;26: 211–215. doi:10.1097/WNR.0000000000000330

38. Rabut C, Yoo S, Hurt RC, Jin Z, Li H, Guo H, et al. Ultrasound Technologies for Imaging and Modulating Neural Activity [Internet]. Neuron. Cell Press; 2020. pp. 93–110. doi:10.1016/j.neuron.2020.09.003

39. Folloni D, Verhagen L, Mars RB, Fouragnan E, Constans C, Aubry JF, et al. Manipulation of Subcortical and Deep Cortical Activity in the Primate Brain Using Transcranial Focused

Ultrasound Stimulation. Neuron. Cell Press; 2019;101: 1109-1116.e5. doi:10.1016/j.neuron.2019.01.019

40. Verhagen L, Gallea C, Folloni D, Constans C, Jensen DEA, Ahnine H, et al. Offline impact of transcranial focused ultrasound on cortical activation in primates. Elife. eLife Sciences Publications Ltd; 2019;8. doi:10.7554/eLife.40541

41. Kubanek J, Brown J, Ye P, Pauly KB, Moore T, Newsome W. Remote, brain region-specific control of choice behavior with ultrasonic waves. Sci Adv. American Association for the Advancement of Science; 2020;6. doi:10.1126/sciadv.aaz4193

42. Pasquinelli C, Hanson LG, Siebner HR, Lee HJ, Thielscher A. Safety of transcranial focused ultrasound stimulation: A systematic review of the state of knowledge from both human and animal studies [Internet]. Brain Stimulation. Elsevier Inc.; 2019. pp. 1367–1380. doi:10.1016/j.brs.2019.07.024

43. Di Biase L, Falato E, Di Lazzaro V. Transcranial Focused Ultrasound (tFUS) and Transcranial Unfocused Ultrasound (tUS) neuromodulation: From theoretical principles to stimulation practices. Front Neurol. Frontiers Media S.A.; 2019;10. doi:10.3389/fneur.2019.00549

44. Legon W, Ai L, Bansal P, Mueller JK. Neuromodulation with single-element transcranial focused ultrasound in human thalamus. Hum Brain Mapp. John Wiley and Sons Inc.; 2018;39: 1995–2006. doi:10.1002/hbm.23981

45. Lee W, Kim H, Jung Y, Song IU, Chung YA, Yoo SS. Image-guided transcranial focused ultrasound stimulates human primary somatosensory cortex. Sci Rep. Nature Publishing Group; 2015;5. doi:10.1038/srep08743

46. Lee W, Kim HC, Jung Y, Chung YA, Song IU, Lee JH, et al. Transcranial focused ultrasound stimulation of human primary visual cortex. Sci Rep. Nature Publishing Group; 2016;6. doi:10.1038/srep34026

47. Lee W, Chung YA, Jung Y, Song IU, Yoo SS. Simultaneous acoustic stimulation of human primary and secondary somatosensory cortices using transcranial focused ultrasound. BMC Neurosci. BioMed Central Ltd.; 2016;17. doi:10.1186/s12868-016-0303-6

48. Hameroff S, Trakas M, Duffield C, Annabi E, Gerace MB, Boyle P, et al. Transcranial ultrasound (TUS) effects on mental states: A pilot study. Brain Stimul. Elsevier; 2013;6: 409–415. doi:10.1016/j.brs.2012.05.002

49. Legon W, Bansal P, Tyshynsky R, Ai L, Mueller JK. Transcranial focused ultrasound neuromodulation of the human primary motor cortex. Sci Rep. Nature Publishing Group; 2018;8. doi:10.1038/s41598-018-28320-1

50. Legon W, Bansal P, Ai L, Mueller JK, Meekins G, Gillick B. Safety of transcranial focused ultrasound for human neuromodulation [Internet]. bioRxiv. bioRxiv; 2018. p. 314856. doi:10.1101/314856

51. Bystritsky A, Korb AS. A Review of Low-Intensity Transcranial Focused Ultrasound for Clinical Applications [Internet]. Current Behavioral Neuroscience Reports. Springer; 2015. pp. 60–66. doi:10.1007/s40473-015-0039-0