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Transcranial Focused Ultrasound stimulation of the primary visual cortex in humans

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Objectives
Transcranial Focused Ultrasound (FUS) has been suggested as a new non-invasive modality of regional brain stimulation, with potential to be more spatially-selective and to reach deep cortical/subcortical areas compared to the conventional methods of transcranial magnetic stimulations (TMS) or transcranial direct current stimulation (tDCS). In humans, low-intensity FUS sonication has been demonstrated to temporarily change the neural activities in the primary somatosensory cortex (SI), based on the observations of subjective sensory manifestations and electrophysiological responses. However, functional neuroimaging evidence of increased neural activity in the stimulated region, as well as the associated network-wide brain responses, has not yet been shown in humans. Here, we administered stimulatory FUS to the primary visual cortex (V1) as guided by the individual-specific neuroanatomy. Concurrent functional MRI was acquired to assess the brain regions that were activated due to the stimulation.
Methods
19 healthy volunteers (five females, ages 20–45, average 26.1 ± 5.4 yrs) participated, and all procedures were conducted under the approval of the Institutional Review Boards of both the Catholic University of Korea and Korea University. Functional MRI (fMRI; for mapping of the visual areas) and cranial CT were obtained from each participant to provide the individual-specific V1 location for sonication planning/targeting. Then, in a separate session, an MR-compatible sonication setup (270 kHz, single-element FUS transducer with radius-of-curvature of 30 mm) was used to deliver FUS to the V1 under a clinical 3-T MR scanner for the image-guidance and the simultaneous acquisition of fMRI data. Separate from the FUS-fMRI session, electroencephalographic (EEG) potentials elicited by the FUS stimulation were also measured. We used a pulsing scheme having a sonication duration of 300 ms with a tone-burst-duration of 1 ms repeated at a pulse repetition frequency of 500 Hz (yielding a 50 % duty cycle). The incident acoustic intensity at the FUS focus was 16.6 W/cm2 Isppa. Retrospective numerical simulation of the transcranial acoustic wave propagation was performed proximal to the sonicated area to estimate the *in situ* acoustic intensity and spatial accuracy of sonication.
Results
Simultaneous acquisition of fMRI during FUS sonication to the V1 revealed the elicited activation not only from the sonicated brain area, but also from the network of regions involved in visual and higher-order cognitive processes. Accompanying phosphene perception was also reported. The EEG responses showed distinct peaks associated with the sonication, having similarities with the classical visual evoked potentials (VEP) generated by photic stimulation. The procedures did not induce any discomforts or adverse effects from the participants, based on the subjective reporting and neuroradiological/neurological examinations. Retrospective numerical simulation of the transcranial FUS suggested the variability in individual responsiveness to the stimulation.
Conclusions
Simultaneous fMRI acquisition during FUS application to the V1 revealed the functional neuroimaging-based evidence in humans that the FUS stimulation activates the sonicated brain area and concurrently elicits the associated phosphene perception. Successful stimulation of the V1 was also supported by the presence of the evoked EEG potentials associated with FUS. The individual variability in responsiveness to the stimulation suggested needs for an elaborate image-guidance.

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Focused Ultrasound modulation of visual search performance and associated EEG in monkeys

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Objectives
Focused ultrasound (FUS) is a promising tool for neuromodulation because of its noninvasivness and better spatial precision compared to other noninvasive methods, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS). FUS neuromodulation has been demonstrated in multiple animal models, including a prior study where ultrasound was applied transcranially over macaque frontal eye field (FEF) to influence saccade response time in an anti-saccade task. In this work, we applied FUS through a craniotomy over the macaque FEF while measuring saccade response times and EEG signals associated with selective attention.
Methods
A single element focused transducer was positioned through a craniotomy over FEF, a cortical area that plays a key role in the eye movement and attention systems. FUS stimulation was applied during a complex visual search task where the monkey was required to shift its gaze to a target among distractors. We alternated blocks of trials with or without FUS stimulation (300 ms of pulsed FUS with a 50 % duty cycle starting 150 ms before search display onset, center frequency 500 kHz, repetition frequency 2 kHz, pulse duration 0.25 ms, peak negative pressures of 250 kPa or 425 kPa, warming of brain tissue < 1.5 °C). Saccade response time and intracranial EEG recordings were acquired in two monkeys performing 9 sessions each.
Results
In both monkeys, event-related potentials (ERPs) associated with selective attention (N2pc) were significantly reduced during stimulation with both intensities. FUS stimulation attenuated the N2pc over the entire session block, rather than on a trial-by-trial basis. In one monkey with a craniotomy positioned directly over FEF, the mean saccade response times were reduced by 5 ms by FUS stimulation at 425 kPa ($p < 0.001$) when the target appeared in the upper hemifield contralateral to the FUS stimulation, while another animal with a craniotomy more ventrally did not show such a systematic behavioral modulation.
Conclusions
We are continuing to explore potential spatial relationships between stimulation location and behavioral modulations in ongoing work. Overall, our findings demonstrate prolonged FUS modulation of attention ERPs and suggest potential spatial selectivity based on the location of stimulation.

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Ultrasound-mediated modulation of motor and ocular responses in anesthetized mice in vivo

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Objectives
Focused ultrasound has been identified as a non-invasive technique for modulating brain activity. Most studies involving sedate rodents utilize frequencies in the kilohertz-range, which allow for optimal transmission of acoustic power through the skull. The tradeoff with using lower frequencies involves producing larger acoustic foci and resultant poor target-specificity. Megahertz-range frequencies can therefore be used to improve target-specificity. This study demonstrates that Focused Ultrasound in the megahertz range can be used to evoke motor and ocular responses in mice under deep anesthesia by targeting cortical and subcortical structures, respectively.

Contralateral-paired hind limb movements were observed when stimulating cortical regions, demonstrating the ability of megahertz-range FUS to stimulate activity in highly-targeted regions. Additionally, pupil dilation was observed when deep-seated anxiety-related structures were targeted, demonstrating the ability of FUS to modulate activity in a small subcortical structures.

Methods

For this study, wild-type adult male mice were anesthetized with intraperitoneal injections of sodium pentobarbital (65 mg/kg) and fixed in a stereotaxic frame. A single-element FUS transducer with fundamental frequency of 1.94 MHz was fixed to a 3D positioning system for accurate navigation through the brain. A 6x6 mm grid centered +2 mm anterior of the lambda skull suture was sonicated in a random order using a center frequency of 1.9 MHz, pulse repetition frequency of 1 kHz, 50 % duty cycle, 1 second pulse duration, 1 second inter-pulse interval for a total of 10 pulse repetitions. The acoustic pressure applied was varied in order to evaluate thresholds for eliciting physiological responses like motor movement, eye movement, or pupil dilation. Motor movements were validated using video recordings and intramuscular electromyography recordings from the biceps femoris in both hind limbs. Pupil movement and dilation from subcortical modulation were evaluated using a high-resolution camera aimed at the right eye and frame-by-frame processing technique.

Results

The minimum peak rarefactional pressure required to elicit hind limb movements was 1.45 MPa when targeting cortical regions, calibrated using an excised mouse skull. Higher pressures increased the success rate from 20 % (at the 1.45 MPa threshold) to 70 % (1.79 MPa) (Fig. 25). Targeting eye-motor and anxiety-related regions of the brain elicited eye movements and pupil dilations up to 20 %. Sonicating the superior colliculus resulted in both eye movement and pupil dilation at a lower threshold pressure (1.20 MPa) than the hippocampus and locus coeruleus, which required pressures greater than 1.80 MPa. A histological evaluation performed in five mice at 1.93 MPa and 3 MPa peak rarefactional pressure resulted in no red blood cell extravasation (Fig. 26).

Conclusions

This study successfully demonstrated that megahertz-range Focused Ultrasound can be used to elicit motor and ocular responses with high specificity in mice *in vivo*. It was also shown that the success rate of stimulation increased with acoustic pressure for motor movements associated with cortical modulation but depends greatly on the region of the brain targeted. These findings emphasize the complex and yet to be determined mechanism of action involved in ultrasonic neuromodulation.

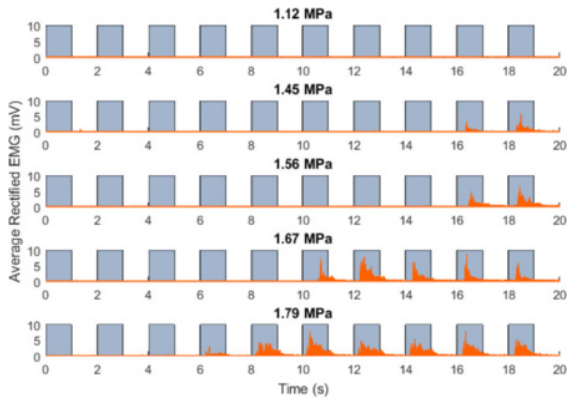

Fig. 25 (abstract A26). Evaluation of the pressure threshold when applying FUS to location within the somatosensory cortex. This location resulted in contralateral hind-limb movement relative to the sonication site

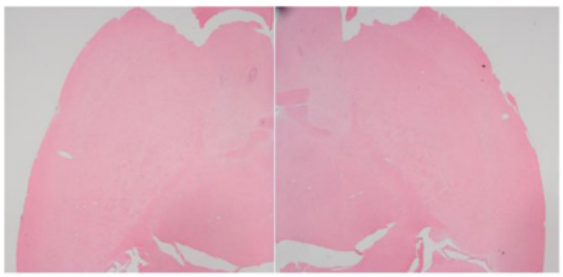

Fig. 26 (abstract A26). Histological evaluation of brain at 1.93 MPa (left) and 3 MPa (right) revealed now red blood cell extravasation

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Non-invasive neuromodulation via targeted delivery of neurotransmitter chemicals

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Objectives

Focused ultrasound (FUS)-microbubble treatment has been used to open the Blood-Brain Barrier (BBB) for targeted delivery of a wide variety of therapeutics. Here we propose to deliver neurotransmitter chemicals such as GABA or glutamate for the purpose of non-invasive neuromodulation. These chemicals function to transmit or suppress signals across the chemical synapses that connect neurons in the brain. This novel approach affects signaling between neurons, as opposed to existing neuromodulation techniques that affect the transmission of electrical signals along neurons. Such an approach could be an important new complimentary tool for basic neuroscience or lead to new therapies for neurological disorders.

Previously, we used electrophysiology measurements to demonstrate functional blockade via BBB disruption and GABA administration. Here we present initial results demonstrating the proof of concept in a rodent model using delivered GABA to modulate neuronal activity and functional MRI to measure the effects.

Methods

Sprague-Dawley rats underwent bilateral hindpaw electrical stimulation (1-5 mA, 0.3 ms duration, 2 Hz) to elicit a functional response of the somatosensory network. Varying levels of GABA were systemically injected under conditions No BBB opening and BBB opening. Functional activity in the thalamus and S1 was measured using fMRI to quantify any effects of neuromodulation.

BBB opening: Microbubbles injected (Optison, 200 μl/kg), 274 kHz dual aperture transcranial FUS with 32 ms bursts applied at 4 Hz for 60 seconds.

GABA delivery: Systemic tail vein bolus injection in doses from 10 mg/kg to 50 mg/kg.

fMRI: Images acquired on a Bruker 7 T scanner with a single shot EPI sequence (TR = 1.5 s, TE = 18 ms, 18 slices, 300 images). Stimulation performed in a 40 s OFF, 20 s ON block design over 7.5 total minutes. T-scores obtained using general linear model analysis in SPM 12.

Results

BBB Closed: Fig. 27 shows activation results in S1 for the case of No BBB opening. Compared to the baseline case of No GABA injected, a GABA injection of 10 mg/kg showed significant decrease in activity ($p < 0.05$) but GABA injections of 25 mg/kg and 50 mg/kg did not.

BBB Open: Fig. 28 shows activation results in the thalamus for the case of BBB opening. BBB opening was targeted, and confirmed through gadolinium imaging, in the right hemisphere. Bilateral activation was seen in the thalamus for the baseline case of No GABA