Image-guided modulation of regional brain function mediated by focused ultrasound

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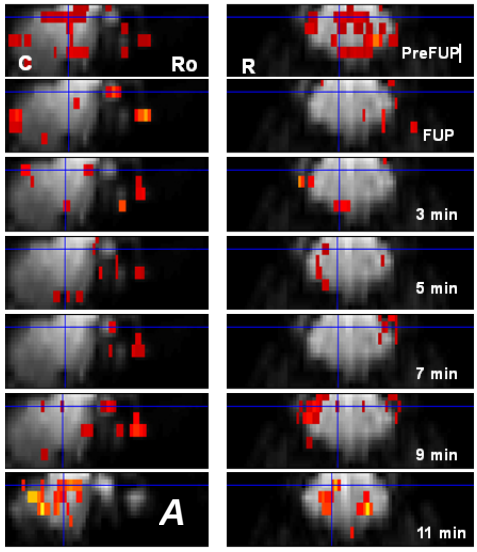
Introduction: Non-invasive and controllable modulation of regional brain activity may open new avenues for various clinical applications ranging from functional brain mapping to treatment of numerous neurological and psychiatrical disorders. Focused ultrasound (FUS) technique allows for the non-invasive delivery of acoustic energy to a localized tissue area, measuring few millimeters in diameter, depositing mechanical or thermal energy, which can be characterized by imaging modalities such as MRI. Using FUS sonication, selective modulation of regional neural activity was sought after, and we found evidence that FUS, as administered in train of pulses, resulted in reversible modulation of cortical activity in animal model.

Method: New Zealand white rabbits (n=5; all male, body weight 3.5-4 kg) were used in this preliminary experiment. In order to eliminate the effects of skull in acoustic wave propagation, the piece of skull (oval shape, approximately 1.5 x 2 cm) was removed under anesthesia. The animals were allowed to recover from the surgery for two weeks while any air trapped under the skin during surgery was dissolved. All experiments was conducted in a 3 Tesla MRI scanner (GE) using a surface coil (2 inch diameter) for RF transmission and detection. For the sonication, we used the 690KHz ultrasound transducer, operated at 25, 50 and 350 W/cm^2 (in terms of temporal peak intensity) as a short bursts (0.5ms or 1ms- long; *i.e.* focused ultrasound pulse: FUP) with the separation of an inter-pulse-interval of 1, 10, and 50 ms. The various durations sonication was used 9, 18 and 27 sec.

Three animals were immediately sacrificed upon FUP procedure with the systemic injection of Trypan Blue to examine the presence of BBB disruption and any acute changes in the brain tissue. Two animals were allowed to survive after the FUP for additional one week to monitor any adverse behavioral changes associated with the procedure. The brain was extracted underwent histological analysis using H&E stain to examine the presence of hemorrhaging or tissue damage. No ultrasound contrast agent was used in the procedure.

A gradient echo (single-shot) EPI sequence was used (TR/TE=1000/40ms, FA=90°, 64×64 matrix, 8×8cm FOV, 64x64 image matrix 3 mm slice thickness; no slice gap; voxel size=1.25 x 1.25 x 3 mm^3), and imaged most of the brain in the axial orientation to obtain the blood-oxygenation-level-dependent (BOLD) fMRI signal. Using block-based design to deliver the interleaved period of visual stimulation (LED strobe driven at 3Hz, 27 s long). The rabbit's visual was identified using pixel-by-pixel temporal correlations with the canonical hemodynamic responses. The areas showing the high temporal correlation was statistically thresholded (p<0.001) to isolate the site of activation. Temperature changes to the region were non-invasively measured right after fMRI-sonication experiment, by detecting changes in the water proton resonant frequency (PRF) [1]. Real-time fMRI (rtfMRI) platform [2] allowed the monitoring of responses from the sonication, and enabled the testing of different combinations of sonication parameters (in *n*=2 animals).

Results Since we wanted to use the lowest power which produces the observable effects, FUP (0.5ms duration and 10 msec inter-pulse-interval) at 50W/cm^2 intensity was used in the subsequent experiment to confirm the observed effects from rtfMRI sessions. We adopted a 'trial-based' fMRI paradigm, to simulate the effects of evoked-potential measurement scheme. We applied three different durations of FUP, *i.e*. 9, and 18 sec, being synchronized with the duration of the visual stimulation. Multiple fMRI sessions (*n*=7; Figure) were conducted to obtain the activation map during (1) baseline state (without FUP; preFUP) and (2) FUP application. Five of those fMRI sessions were administered to monitor the progression of BOLD signal responses and recovery of the activation after the application of the FUP in every 2 minute. The data was processed using SPM2 software to detect the activation using general linear model, and thresholded at p<0.001. As demonstrated in the Figure, robust activation in the visual cortex (in blue cross hair) was suppressed during and after the FUP application, and remained suppressed for more than 11 min. The complete level of BOLD contrast was observed after about 15 minutes post FUP. Based on the real-time fMRI data, we have also found that a shorter (less than 5 sec) FUP application elevated the BOLD signal level, which indicate the evidence of increased excitability of the brain. Post FUP histological analysis showed that there was no presence of tissue damage and BBB disruption across the tested animals. MR thermometry data indicated that there was no rise in local and global tissue temperature during the application of the FUP application.



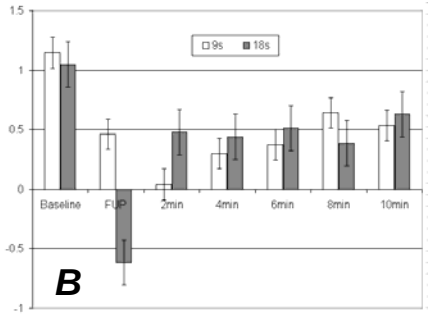


Figure ***(A)*** *The time-progression of visual activation map (p<0.001) before, during, and after the 18 sec of FUP application from one animal. [C: Caudal, Ro: Rostral, and R: Right]* ***(B)*** *The time-progression of BOLD signal contrast (in %) before and after the FUP application (n=3) for the duration of 9 sec (white) and 18 sec (gray).*

Discussion: We demonstrated that local visual activation can be successfully modulated for more than 10 min after the application of FUP, in the absence of temperature changes in tissue. The maximum mechanical index (an estimate of maximum amplitude of pressure pulse) at this energy level was 1.17, lower than the current FDA limit (1.9) for ultrasound imaging equipment for clinical use. These results indicate that the FUP may safely induce the desired transient modification of regional cortical activities reversibly.

Reference: [1] Ishihara et al. Magn Reson Med (1995) 34: 814-23. [2] Yoo et al. Neuroreport (2002) 13:1377-81.