Functional MRI reveals the reliable brain modulation effect induced by focused ultrasound

HSIN-YI LAI[1,2], PO-CHUN CHU[3], HSIANG-WEI HU[4], YOU-YIN CHEN[5], YEN-YU IAN SHIH[6], and YU-CHENG PEI[1,2]

[1]School of Medicine, Chang Gung University, Taoyuan, Taiwan, [2]Department of Physical Medicine and Rehabilitation, Chang-Gung Memorial Hospital, Taoyuan, Taiwan, [3]Electrical Engineering, Chang Gung University, Taoyuan, Taiwan, [4]Department of Biomedical Engineering, National Yang-Ming University, Taipei, Taiwan, [5]National Yang-Ming University, Taipei, Taiwan, [6]Department of Neurology, Biomedical Research Imaging Center, University of North Carolina, Chapel Hill, NORTH CAROLINA, United States

INTRODUCTION: Focused ultrasound (FUS) co-administrated with intravenously circulating microbubbles is a novel non-invasive method for temporarily disrupting the blood-brain barrier (BBB) that has been applied in the drug deliver for the treatment of brain tumor[1,2]. However, the FUS may result in undesired brain damage, and the optimal acoustic pressure of FUS remains controversial. A previous MRI contrast study indicated that BBB disruption reached a 50% enhancement at acoustic pressure of 0.4 MPa[3]. Functional magnetic resonance imaging (fMRI) could be used to characterize brain modulation effect induced by a variety of FUS acoustic pressure. The goal of the present study was to characterize the FUS-induced changes of hemodynamic responses for optimizing the acoustic pressure of FUS. A previously histological study indicated that FUS with acoustic pressures of 0.4 MPa is an optimum intensity due to maximum BBB disruption with a few areas of brain tissue erythrocytes[4]. However, the present study characterized the time course of functional recovery by observing the changes of fMRI responses with varying FUS acoustic pressures and the results are incompatible to those observed in previous studies by finding that 0.3 MPa is a reliable transmitting acoustic pressures for brain modulation.

METHODS: Adult male Sprague Dawley rats (300–350 g) underwent 0.1 mg/kg Dexdomitor® anesthesia (n=15 for fMRI, n=24 for histology) and scalpremoval before ultrasound induction. SonoVue® SF6-coated ultrasound microbubbles (2-5 μm mean diameter, 10 μl/kg) were IV administered with 0.35 ml of saline solution containing 0.01 ml heparin. FUS with acoustic pressures of 0.4 MPa or 0.3 MPa was transmitted to the left forelimb area of the somatosensory (S1FL) cortex (1 mm posterior and 4 mm lateral to the bregma) at a penetration depth of 1-2 mm under the skull using a focused ultrasound transducer (IMASONIC, France; diameter=60 mm, radius of curvature=80 mm, frequency=400 kHz and electric-to-acoustic efficiency = 70 %). In the control group, FUS with acoustic pressures of 0.4 MPa was transmitted to S1FL without microbubbles injection. FMRI was performed in a Bruker 7T system using a gradient-echo EPI sequence (BW=200 kHz, TR/TE=2000/20 ms, Matrix=80x80, FOV=2.5x2.5 cm2, slice thickness=1 mm). Blood oxygen-level dependent (BOLD) responses elicited by forepaw electrical stimulation were obtained before and after FUS to observe the time course of suppression induced by FUS. FMRI scans were acquired for 30 repetitions, during which stimulation was applied in the OFF-ON-OFF blocks followed by a 3-minute inter-scan resting period. The period of each OFF/ON black was 20 seconds. The stimulation paradigm was a regular bipolar square-wave current of 6 mA with a pulse width of 0.2 ms at a frequency of 12 Hz. Two to four repeated trials were performed to improve measurement accuracy and optimize SNR. In order to confirm the histological changes induced by FUS, rats were sacrificed at 0-day, 2-day and 7-day post-FUS and the brain slices were stained with hematoxylin and eosin (HE). The areas of red blood cell (RBC) that reflect the level of brain injury induced by FUS was counted in the FUS sites of each brain slice.

RESULTS & DISCUSSION: Compared to the control group, 0.4-MPa FUS exposure suppressed BOLD responses in the S1FL cortex elicited by forepaw electrical stimulation in 2 hour follow-up and the effect could last for 7 days ($p < 0.05$). 0.3-MPa FUS exposure also suppressed BOLD responses in 2 hour follow-up, but the suppression was non-existence after 2 days following FUS (Figs 1A-B). Histological results showed that the 0.4-MPa FUS induced significant microscopic hemorrhage, while the 0.3-MPa FUS induced minimal or no microscopic hemorrhage (**Fig. 1C-D)**. These results showed that 0.3 MPa could be the optimal acoustic FUS pressure for producing a reversible and local brain modulation effect.

CONCLUSION: This present study proposed a novel non-invasive, reversible and localized brain modulated method. 0.3 MPa could be the optimal acoustic FUS pressure for producing a reversible and local brain modulation effect.

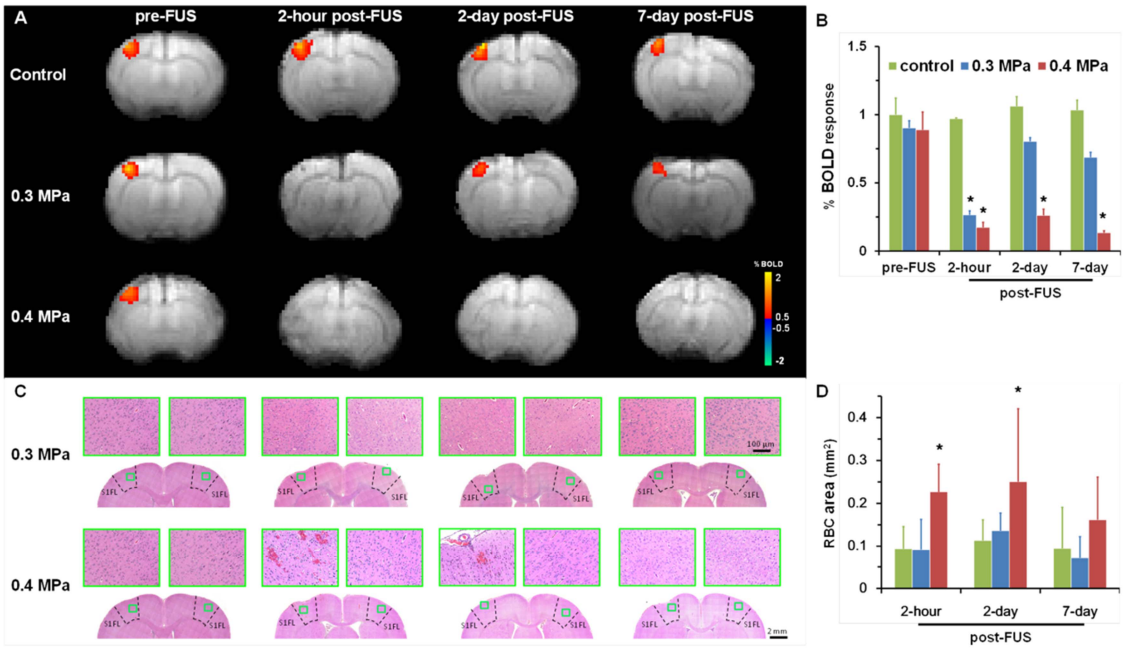

Fig 1. BOLD fMRI and HE staining of FUS-BBB disruption. **(A)** Group-averaged BOLD activation maps (n=5 for each group). Responses were mainly located in the S1FL cortex. **(B)** Time course of BOLD response before and after FUS transmission. **(C)** Example histology slices using hematoxylin and eosin (HE) staining method. **(D)** The red blood cell (RBC) area in the S1FL cortex after FUS transmission.

REFERENCES: 1. Po-Chun Chu et al., Pharmacodynamic analysis of magnetic resonance imaging-monitored focused ultrasound-induced blood-brain barrier opening for drug delivery to brain tumors. Biomed Res Int. 2013; 2013:627496. 2. Konofagou E. et al., Mechanism, monitoring, and drug delivery of the ultrasound-induced blood-brain barrier opening. J Acoust Soc Am. 2013; 134(5):4089. 3. Hynynen et al., Local and reversible blood–brain barrier disruption by noninvasive focused ultrasound at frequencies suitable for trans-skull sonications Neuroimage. 2005; 24(1):12-20. 4. Sheikov N. et al.,Focal disruption of the blood–brain barrier due to 260-kHz ultrasound bursts a method for molecular imaging and targeted drug delivery. J Neurosurg. 2006; 105(3):445-54.