Functional ultrasound (fUS) reveals neurovascular response coupled with motor response evoked by focused ultrasound (FUS) neuromodulation in mice

Background, Motivation and Objective. Focused ultrasound (FUS) can modulate excitatory and inhibitory neurons in the central (CNS) and peripheral nervous system (PNS). Earlier FUS studies on CNS have shown that FUS can casually evoke motor responses in mice. However, they lack spatiotemporal dynamics of the FUS-elicited neural activity which is critical in order to determine which brain regions or network are indeed activated and associated with the subsequent motor responses. We herein leveraged functional ultrasound (fUS) imaging to monitor neurovascular responses simultaneously with FUS targeting the sensorimotor cortex and subcortex in order to elicit behavioral responses in anesthetized mice. The objectives of this study were to 1) image the neurovascular responses while FUS induces motor responses and 2) correlate the FUS-evoked hemodynamic responses and the FUS-induced motor responses.

Statement of Contribution/Methods. To that end, we employed a 128-element linear imaging transducer (L22-14vXLF; Vermon) and an ultrasound research system (Vantage 256 HF; Verasonics) to perform displacement and fUS imaging. A single-element FUS transducer (H-215; 4 MHz, SonicConcepts) was used and axially aligned with the imaging transducer. Two female C57BL/6J mice ages 8-12 weeks were used and under anesthesia using ketamine/xylazine (100mg/kg and 10mg/kg) followed by craniotomy, imaging and FUS. During FUS modulation, electromyography (EMG) signals were collected to record FUS-elicited muscle activity from tibialis anterior muscle and tail. We targeted the sensorimotor cortex using displacement-guided FUS pulses with a duration of 80 ms and peak negative pressures from 1.69 to 3.39 MPa. To induce cerebral blood volume (CBV) response to FUS, 10 FUS pulses with a pulse repetition frequency (PRF) of 1 Hz were applied. A hemodynamic activation map was generated based on the Pearson's correlation between CBV signals and binary stimuli signals. To correlate CBV and motor responses, a two-tailed nonparametric Spearman correlation and linear regression were performed. (peak CBV change and activation area vs. peak EMG amplitude)

Results/Discussion. FUS evoked paw movement and/or toe twitches with tail movement (Fig B, right) at 2.54 and 3.39 MPa under adequate anesthesia (very mild paw twitches when pinched). Simultaneous fUS imaging revealed FUS-evoked hemodynamic activation (i.e. CBV increase) at the motor cortex and thalamus (Fig A, left). The activation area was in good agreement with FUS displacement field (>1μm). No significant activation or behavioral response was observed at 1.69 MPa (Fig. A, right). CBV changes at motor cortex increase with FUS pressure, which coincides with stronger motor responses (Fig. B, left). We found a significant correlation (r=0.94) between CBV increase and peak EMG amplitude, but not significant between the size of activation area and the peak EMG amplitude (Fig. C). In sharp contrast, sub-millimeter off-target FUS modulation resulted in no motor responses, indicating the observed motor responses are not due to confounding effect of FUS such as unintended auditory and tactile stimuli from FUS as reported by others under light isoflurane anesthesia. In conclusion, we successfully imaged the neurovascular response via fUS while FUS induces motor responses and CBV peaks at 4s post-FUS. We found the positive correlation between peak CBV and EMG responses, indicating the neurovascular response was indeed associated with the subsequent motor response.