Functional Ultrasound Imaging for Visualization of Rat Brain Activation in Response to Pharmacologically Induced Tremor and its Suppression

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Essential tremor is the most frequent form of pathologic tremor and one of the most common adult-onset neurologic impairments. Pharmacological interventions only help about 50% of the patients with tremor. The development of new therapies has been hampered by a lack of knowledge about tremor pathophysiology and the lack of a validated preclinical model for evaluating potential tremor-suppressing drugs. In this study, we hypothesized that functional ultrasound (fUS) can allow robust assessment of neural activation and mapping of correlated networked-brain activity associated with tremor and pharmacology based tremor suppression.

Harmaline induced tremor experiments were conducted on 6 adult male rats, of which 3 were treated with tremor suppressant drug, propranolol. Drugs were injected intraperitoneally. Imaging data was acquired in both sagittal and coronal planes after limited craniotomy with a high frequency probe (L22-14v). Plane wave based fUS images were acquired every 3 sec, for 4 hours, with 30 minutes of baseline recording prior to drug injection. Corresponding electrophysiology results were obtained on 4 adult male rats at motor cortex (MC) and ventral-lateral thalamus (VLT).

Using fUS imaging on anesthetized rats, we could successfully visualize and quantify tremor activity in the brain, and map correlated activations at high spatial and temporal resolutions (Fig. 1). A steady increase in the brain activity was observed in the MC and VLT regions, which subsequently decreased as the effect of the drug subsided with time. The results obtained from fUS imaging displayed strong activation in the MC and VLT, and particularly, the activation in MC was significantly higher. Further, suppression of tremor using propranolol was robustly visualized using fUS imaging. These results were consistent with literature and those obtained using electrophysiology.

In conclusion, the encouraging results from our preliminary preclinical study demonstrate the feasibility of fUS imaging for visualizing drug-induced tremor activity in rat and provide the potential of fUS imaging to assess the functional mechanisms of subsequent pharmacological intervention.

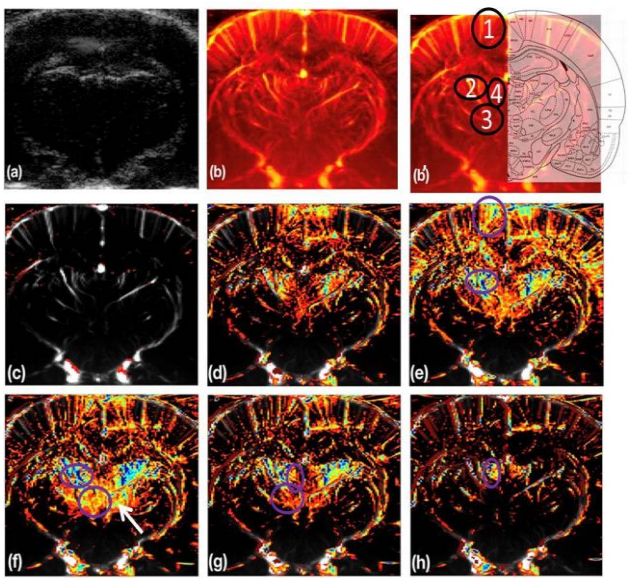

Figure 1. Activation map of fUS imaging by harmaline injection. (a) The ultrasound B-mode image of the rat brain (b) Microvasculature power Doppler image (1- motor cortex, 2- lateral dorsal thalamus, 3- ventral thalamus and 4- medial dorsal thalamus) (c-h) Images at different time points (c- 10 min, d- 65 min, e- 8 min, f- 110 min, g- 125 and h- 160 min after harmaline injection). Notably, brain-wide sequential activation was identified by fUS imaging (activation started from area listed as (1) and moved to (2) through (4)).