Research Funding Agreement Between
The Focused Ultrasound Foundation
and
Vanderbilt University
Noninvasive targeted neuromodulation and functional imaging in behaving macaques
Progress report: July 29, 2016

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Aim 1) Optimize MR acoustic radiation force imaging (MR-ARFI) and image-guided insonation through an *ex vivo* macaque skull filled with phantom material to ensure accurate localization of the frontal eye field.

We have reported our progress on this aim in the prior two reports. This work was presented as a podium talk at the 2015 BMES annual meeting and will be presented at the upcoming FUS Foundation meeting. Currently, we are creating a workflow to efficiently guide the ultrasound beam, which we are implementing in 3D Slicer. We will make associated software available to other researchers.

Aim 2) Confirm effectiveness of ultrasound to elicit or modulate behavioral responses in awake, behaving monkeys.

We have outlined our progress in the prior report and will present this work at the FUS Foundation meeting in 2016. We are analyzing data from a 3rd animal and have prepared a submission to Current Biology.

3) Confirm effectiveness of ultrasound to elicit or modulate fMRI responses in regions known to be anatomically connected to somatosensory cortex.

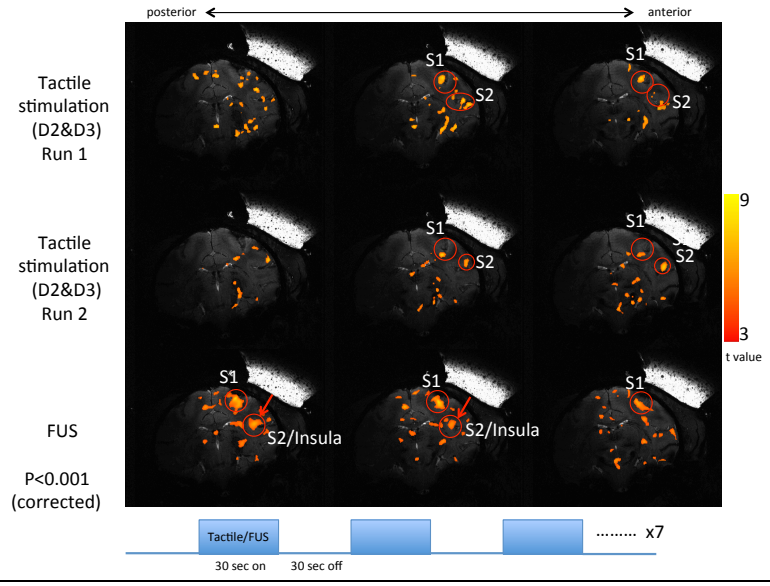

Figure 1. During tactile stimulation of D2 and D3, we have observed robust BOLD fMRI response in S1 and S2 (top two rows). Upon application of focused ultrasound to the S2/insula region, we see BOLD fMRI changes in the stimulated region as well as S1 (bottom row). During the experiments, stimulation (either vibrotactile or ultrasound stimulation at 250 kHz) was applied in 30 second intervals (bottom row).

We have applied ultrasound to the macaque S1/insula region during fMRI using the stereotactic frame developed previously as part of this project (Figure 1). The system holds the monkey in place in the sphinx position within our human 7T MRI and can accommodate the Sonic Concepts transducer used in Aim 1. We detected reproducible

tactile stimulus evoked BOLD fMRI activations in expected areas S1 and S2 regions. When targeting the ultrasound beam at S2/insula region, fMRI signal changes were detected at the stimulated region as well as in S1 region. Stimulation effects appeared to be robust, and spread on multiple adjacent image slices. Further experimentation will be necessary to assess robustness of the detected BOLD response.

Presentations and publications: The following talks are directly related to the work in this FUS Foundation grant and associated manuscripts have been prepared for submission:

1. Chaplin V, Clements L, Miga M, Caskey CF. “Development of an Optically-guided System for Transcranial Ultrasound Neuromodulation” BMES 2015 Annual Meeting. *Accepted as oral presentation.*

2. Caskey CF, “Development and Evaluation of Technology for Ultrasonic Neurostimulation” Kavli Futures Symposium, Invited Talk, June 2015.

3. Caskey, C. F., Zinke, W., Cosman, J., Shuman, J., Schall, J. (2016), “Ultrasound stimulation in the frontal eye field modulates visual search and associated EEG in monkeys," *IEEE Ultrasonics Symposium (IUS), 2016* (Upcoming oral presentation).

4. Zinke, W., Cosman, J., Shuman, J., Schall, JD, Caskey, C.F. “Focused ultrasound over frontal eye field of macaque monkeys: Modulation of visual search performance and EEG index of attention” *Society for Neuroscience* (Upcoming poster presentation).

Follow-on funding:

Title: “Neuron selective modulation of brain circuitry in non-human primates”
PIs: Charles F. Caskey, William A. Grissom, Limin Chen
Description: An ultrasound transducer specifically designed for neurostimulation will be integrated into a high field (7T) human magnetic resonance imaging system and used to modulate the function of the well-studied visual and somatosensory systems of non-human primates. Using a mathematical model of ultrasonic interaction with neurons, we will develop acoustic pulses for transcranial stimulation that can stimulate or inhibit neuron activity. We will quantify the effects of these pulses on neural circuitry, validate the effects with neurophysiological measurements, and concurrently use functional MRI to non-invasively assess brain function at the circuit level.

Grant applications under review:

Title: "Establishing a dose response for ultrasound neuromodulation"
Agency: NIH
PIs: Charles F. Caskey, Limin Chen