Investigating Biophysical Effects of Ultrasound Neuromodulation

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Ultrasound neuromodulation has a broad therapeutic scope including treatment of various neurological and psychiatric diseases. It is a promising technique due to its noninvasive nature, high spatial resolution, and ability to penetrate deep into the brain. Yet, the underlying biophysical mechanisms remain unclear due to inconsistencies across studies, posing a barrier for clinical translation. The Han Lab recently demonstrated that ultrasound transiently increases intracellular calcium in neurons in the mouse brain, but this response does not directly correlate with action potentials. Imaging with genetically-encoded voltage indicators (GEVIs), however, enables direct visualization of membrane potential and neuronal spiking. Furthermore, a preliminary study by Cain et al. obtained significant clinical results with chronic ultrasound stimulation. Building off these studies, we worked towards clinical applicability by using one-photon microscopy to visualize the response to ultrasound of (1) motor cortex interneurons expressing a novel GEVI, SomArchon, and (2) neurons expressing a genetically-encoded calcium sensor, GCaMP. We tested chronic ultrasound parameters on the GCaMP neurons. From identified regions of interest (ROIs) in the video data, we extracted fluorescent traces. In GCaMP neurons, we saw a small percentage of ROIs either positively or negatively modulated with respect to the normalized fluorescence and event density. SomArchon results had higher percentages; most significantly, 40% of PV interneurons' spike rate was negatively modulated. Overall more testing of chronic stimulation is necessary for a robust understanding of underlying mechanisms, but voltage imaging can reveal neural responses to ultrasound that may be unaccounted for during calcium imaging.