April 28, 2025

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Title: In vivo responses to transcranial focused ultrasound neuromodulation in mice

Abstract: Transcranial ultrasound stimulation (TUS) is an emerging noninvasive neuromodulation technique capable of eliciting excitatory, inhibitory, immediate, and sustained neural responses. Despite its promise, clinical implementation remains limited due to an incomplete understanding of how stimulation parameters relate to neural outcomes, making it difficult to achieve intended neuromodulatory effects. A major obstacle in mapping this relationship is auditory activation, which can trigger startle responses that alter network-level activity and complicate the interpretation of TUS-induced neural responses. In this thesis, I use a mouse model to explore strategies for mitigating the auditory confounds to isolate direct effects of TUS neuromodulation at the targeted brain region.

First, to address peripheral auditory activation, I developed and experimentally validated a computational metric that quantifies susceptibility to unintended auditory brainstem responses (ABRs) based on time frequency analyses of TUS signals and auditory sensitivity. This analysis revealed that ABRs, or sharp changes in peripheral auditory activation, can be reduced by: 1) lowering the amplitude of rectangular continuous wave envelopes, 2) increasing the rise/fall times of smoothed continuous wave envelopes, and/or 3) changing the pulse repetition frequency and duty cycle of pulsed waves to reduce the gap between pulses and increase smooth the overall envelope profile. The modulated signals can reduce the confounding auditory-induced startle responses.

Then, I studied the downstream impact on central auditory activation using widefield calcium imaging of the cortex. Contrary to previous findings, clear neural activation was observed at the focus in the visual cortex during sonication. Immediately following sonication, additional activation was found in the retrosplenial and auditory cortices. Notably, no significant changes to central auditory activation were found when peripheral auditory input was reduced by smoothing the waveform, suggesting a non-sensory source of auditory cortex activation from direct TUS neuromodulation. Additionally, I examined sustained effects on visual-evoked responses and found that TUS using high amplitude rectangular waveforms could induce transient yet sustained neural changes on the order of minutes.

These findings demonstrate that while startling peripheral auditory artifacts can be reduced through specific waveform modifications, central auditory activation may still persist. Nonetheless, both immediate and sustained focal neural effects at the targeted sites can be observed and characterized even in the presence of off-target activation. While off-target effects may be difficult to avoid entirely, they can be accounted for their when assessing net neural and behavioral responses. By demonstrating evidence of direct neural changes on the network-level, this work paves the way for precise, reproducible neuromodulatory interventions via TUS.