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Reversible neuroinhibition does not require a thermal mechanism

Dear Editor:

We wish to respond to the recent publication by Darrow et al. titled "Reversible Neuroinhibition by Focused Ultrasound is mediated by a Thermal Mechanism [1]." Specifically, we wish to alert the larger transcranial Focused Ultrasound Sonication (tFUS) community regarding inducing reversible neuroinhibition without thermal changes. Prior research has clearly demonstrated neuroinhibition without the temperature change suggested by Darrow et al. In a study attempting to suppress regional cortical excitability in rabbits, fMRI BOLD was used to monitor neural activity in the visual cortex after LED light stimulation [2]. Focused Ultrasound with a tone burst duration of 0.5 msec, Pulse repetition frequency = 100 Hz, and $I_{sppa} = 3.3$ W/cm^2 successfully suppressed the BOLD signal caused by light stimulation. The authors initially set out to confirm the accuracy of their targeting in rabbits using MR thermometry [3].

MR thermometry is based on the principle that the metrics used in MR-imaging (i.e. spin-lattice relaxation time, spin-spin relaxation time, proton density) are sensitive to temperature changes [3]. Specifically, the equation for measuring change in temperature caused by focused ultrasound stimulation can be given by

$$\Delta T = \frac{\phi(T) - \phi(T_0)}{\gamma \alpha B_0 TE}$$

where $\phi(T)$ is the phase in the current image, $\phi(T_0)$ is the phase of a reference (baseline) image at a known temperature, γ is the gyromagnetic ratio, α is the pulse repetition frequency change coefficient, B_0 is the magnetic field strength, and TE is the echo time. In the case of Yoo et al. [2], the phase difference between the images was not sufficient to produce a reliable measure of temperature difference. The sensitivity of the MR thermometry method they used was 0.3 ± 0.06 °C. In fact, a higher I_{sppa} of 12.6 W/cm^2 that was used on the motor cortex to induce forepaw movement within the same study did not produce a noticeable temperature change. It was only at a much higher I_{sppa} of 23 W/cm^2 that a slight temperature increase of 0.7 °C was observed. As the authors of Yoo et al. state, "This suggests that the thermal mechanism did not contribute to the observed modulation of BOLD signal." [2].

In the case of Yoo [2], MR thermometry failed because of the mechanical and subthermal nature of the ultrasonic stimulation did not result in temperature change detectable by MR thermometry. Prior work done by Korb et al., has shown that the worse-case scenario of low-intensity ultrasound delivered simultaneously with BOLD imaging in the MRI scanner results in heating of no more than a few degrees [4]. There are other examples in the literature which suggest that heating is not required in order to facilitate neuroinhibition, or more generally, neuromodulation [5–7].

With this letter, we wish to emphasize that robust neuromodulatory results can be obtained by using ultrasound in a pulsed fashion at much lower intensities without risk of thermal injury.

Conflicts of interest

NMS declares no interests. MES is the CEO of Sonic Tech and CTO of BrainSonix. AB is the CEO of BrainSonix.

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