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Variations in targeting techniques of focused ultrasound for use in neuromodulation

Dear Editor:

Modern times have seen an increase in the use of focused ultrasound (FUS) for neuromodulation [1]. However, the field has yet to agree upon a way in which FUS should be targeted at deep brain structures.

The most common is the anatomical method, which involves aiming the line orthogonal to the plane of the transducer to point at the desired subcortical target [2]. Then, by tracing the focal depth of the transducer along this line, one can identify the region of the brain currently in the focus of the transducer. Indeed, this gives the origin of the term "MR-guided focused ultrasound." This method is not entirely desirable. One, the focus of the transducer is determined in degassed water, which needless to say, is not like brain tissue. This not only does not account for a loss of energy as the ultrasound travels through the skull, but also does not account for how the focus might change position when the ultrasound waves refract against the human skull. This is due to the different velocity of ultrasound waves in water versus through brain tissue. Individual variation in skull anatomy may exacerbate this difference further [3]. CT scans are needed *a priori* in order to plan out accurate targeting [4]. This drawback also applies to the use of previously acquired MR images with optical tracking devices [5].

If the anatomical method uses geometry to target, then another option for targeting of FUS is to look at how sound travels through the brain. In this technique, transcranial Doppler ultrasound is used to identify a blood vessel adjacent to the desired target [6]. Usually the focus of the stimulator transducer will be large enough that the region around the blood vessel will contain the desired target. This method is imprecise and is far from the best way to target FUS. It is however, the most accurate targeting that can be done outside of, and without an MRI scanner.

The next best method is to use (in post-processing or real-time) the analysis of the blood oxygen level dependent (BOLD)/arterial spin labeling (ASL) signal generated by ultrasound stimulation [6]. An activation on the BOLD/ASL image in the area of the desired target is assumed to demonstrate that brain activity or perfusion was changed in that region. Changes in perfusion or regional activity are however an indirect measurement of ultrasonic effects. It is likely possible that the ultrasound is activating white matter tracts and/or a region upstream from the targeted region, leading to a false signal in the region of interest.

It seems then, that the best targeting technique is to directly look at the displacement of tissue caused by the ultrasound waves, using Magnetic Resonance- Acoustic Radiation Force Imaging (MR-ARFI) [7]. MR acoustic radiation force imaging (ARFI) was developed specifically for use with ultrasound to determine the elastic properties of tissue as affected by acoustic force. Traditionally, tissue displacement located near the ultrasound focus was measured using MR elastography which was cross-correlated with ultrasound imaging across different segments of tissue to produce displacement maps which can be used to differentiate tissue types and tissue health. Since ultrasound is typically a longitudinal wave, it will displace tissue in its path, with displacement linearly related to the peak negative pressure of the wave. At its focus, the transducer will generate the greatest peak negative pressure. As a result, the tissue in the focal region of the transducer will experience the most displacement, which can be measured using MR-ARFI to accurately verify the actual FUS focal point in the brain. MR-ARFI can not only provide data about the focal location of the FUS beam, it can be used to provide feedback for adaptive algorithms for correcting displacement caused by the skull [8], which can help reduce the need for a concurrent CT scan for skull distortion correction. The spatial resolution of MR-ARFI can measure displacement on the order of 10 μm [9] through 2mm, depending on the type of MR scanner and sequence used. This technique is by far the most accurate, but historically has also been extraordinarily challenging. Up until very recently, the ultrasound intensities required to successfully acquire these images were far above what was normally used in human neuromodulation (8). Such intensities lead to damage to tissue, which is desirable in high-intensity focused ultrasound applications, such as non-invasive ablation. Avoiding these effects would be desirable in neuromodulation applications.

With regard to neuromodulation, the most important advance that makes MR-ARFI a meaningful tool for low intensity FUS research is that it does not rely on thermal changes, which would not be expected in low intensity FUS experiments. Additionally, technological advances have made this even more appealing, including advances which have reduced the time required to collect the ARFI data while simultaneously increasing spatial resolution (e.g. through rapid (1.45–3000 ms) MRI acquisition with high signal-to-noise ratio and submillimeter resolution). Very recently, advances have been made that allow for rapid, high resolution MR-ARFI estimation of the FUS beam location with FUS pulses as short as 1.45 ms [10]. While the practical utility of these techniques continues to be developed (e.g. moving away from requiring a 7T magnet and in-house MR sequences), MR-ARFI can currently be used to verify the focal targeting of both high and low intensity FUS. In this vein, recent publications have compared the accuracy of frameless stereotactic optical tracking to MR navigation and MR-ARFI(7) with optimistic findings.

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Great progress has been made in the last five years in increasing spatial and temporal resolution of ultrasound targeting. Given that implementing MR-ARFI is now feasible, this could be a way to ensure that the transducer is targeted at the proper anatomic regions. Furthermore, there is much interest lately in customizing the transducer acoustic lenses to patient's specific neuroanatomy to allow for extremely precise targeting of subcortical structures, which will require a technique such as MR-ARFI for verification. Further work is needed to improve the procedures used during neuronavigation to better the veracity of findings.

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