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Letter to the Editor

Transcranial Focused Ultrasound Stimulation in Dynamic Clinical Settings: Initial Strategy in Schizophrenia and Status Epilepticus

To the Editor-in-Chief—The intent of this letter is to report our initial strategy and experiences delivering Transcranial Ultrasound Stimulation (TUS) for extended periods of time to Schizophrenia (SCZ) and Status Epilepticus (SE) participants. This report is notable since there are ongoing efforts in the field to classify specific ultrasound dose standards and guidelines for human TUS [1]. There is also limited published knowledge on conducting experimental TUS in these types of dynamic and challenging clinical settings [2–4]. Our ongoing pilot studies include SCZ subjects with current psychosis receiving TUS in an outpatient facility and a separate investigation with TUS being delivered to SE patients presenting real-time seizure activity in the intensive care unit (ICU). Our report provides pertinent insights for those considering implementing TUS therapeutic investigations for neurological and psychiatric disorders. We discuss our sonication parameters to inform any regulatory bodies pursuing TUS standards. Practical solutions to the challenges we faced delivering TUS in these clinical settings are also summarized.

According to a recent review of the field [5], the effects of TUS on central nervous system diseases have been investigated in 22 studies and on healthy subjects under controlled lab conditions in 42 studies. Both custom-made focused ultrasound systems and commercial research units have been used to deliver sonication. We use neuronavigation-guided single-element focused transducers (350 kHz, 85 mm aperture, custom) designed to penetrate into deep brain structures or the cortex with focal lengths of 65 and 25 mm, respectively. SCZ subjects receive right Globus Pallidus (GP) sonication (1 active session) given its association with psychosis and treatment response [6]. SE patient sonication is delivered to any epileptic cortical location or to the thalamus (1–2 active sessions back to back) since directly targeting epileptic tissue or epileptic circuitry with TUS has previous been applied [2,8]. We are among a handful of groups [2–4,7,8] recently exploring an extended sonication time or multiple active sessions. Our protocols use an active sonication over 10 min with pulsed parameters (Supplementary Table 1). All free-field calibrations were set to spatial peak pulse average intensity = 60 W/cm^2, or an equivalent spatial peak temporal average intensity of 3 W/cm^2 using 5% duty cycle. Given relevant literature ranges and from our previous experience testing sonication through ex vivo human skull samples [9], we expect the skull attenuates this ultrasound intensity by 50%–85% before reaching brain targets in any given participant. Additional methods such as pseudo CT-driven computational simulation can help further assess tissue temperature and beam behavior in the sonicated regions. We position our transducer and focal point to brain targets through the skull using straight-on alignment without computational-assisted spatial correction. No adverse events have occurred in participants across both studies (7 SCZ and 1 nonconvulsive SE). All participants tolerated partial head stabilization with gel in their hair for 15-min periods.

One of our most challenging tasks was establishing a method for prolonged head stabilization, as we did not use full head restraint or straps to avoid catalyzing subject stress. A very useful solution was using adjustable Velcro Styrofoam head immobilizers. Multiple Styrofoam blocks were used to achieve head stabilization during sitting or supine, while still allowing transducer coupling (Supplementary Fig. 1). Our transducer positioning was achieved by fine-adjustment controls linked between the transducer and a lockable articulating arm. Head-transducer alignment and water bag coupling remained stable over 10-min sonication periods with the target accuracy ensured by using landmarked T2-weighted magnetic resonance imaging (MRI) guided neuronavigation [10]. In SE it was easier to hold the transducer by hand over a removed electroencephalography (EEG) lead location (over the epileptic cortical activity) when there was limited imaging data for neuronavigation or life support systems obstructed the positioning apparatus. Modifying the head stabilizer to hold a subject's head in a lateral or prone position could be a solution to the limitations found during occipital lobe sonication.

Lastly, it is important to consider increased operator and research team stresses in these dynamic working environments. The extra layer of awareness required to set up and operate ultrasound systems in critical care suites or when administering sonication to psychologically complicated subjects can impose unforeseen challenges when executing the lower level technical tasks during sonication. This was especially important during SE in the ICU given the unscheduled working window and limited prep time to prepare for patient-specific brain targets. Overall, being courteous, patient and having continuous communication with participants and the research team contributed to successful sonication sessions.

Protocols for device usage in human subjects were approved as separate and independent studies by New York University Langone Health Institutional Review Board (IRB) for SCZ and the Yale School of Medicine IRB for SE. All research participants provided written informed consent to participate in the ongoing studies. Clinical outcomes for SCZ (NCT05643196) are changes in auditory hallucinations subscale with offline GPi functional connectivity changes measured via functional MRI. SE outcomes (NCT05784805) are epileptiform activity changes measured with surface EEG.

Conflict of interest

The authors report no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ultrasmedbio.2024.12.019.

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