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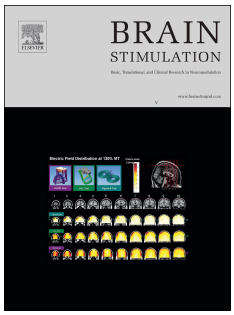

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Ultrasound Neuromodulation – How deep can we stimulate?

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Dear Editor,

A major methodological progress inherent in ultrasound neuromodulation concerns the capability for non-invasive highly focal deep brain stimulation. But – how deep can we stimulate?

The new article by Ham et al. describes enhancement of neuronal target activity with ultrasound neuromodulation in a depth of 12 mm from the reflector (maximum pressure) in a mouse model [1]. This was achieved with a specifically developed sonication system based on the principle of shock wave generation with a dielectric breakdown (DB system). In contrast, Ham et al. did not find upregulation of neuronal target activity with a commercial shock wave system based on an electromagnetic transducer (EM system). EM reached maximum pressure over an extended area in 20-65 mm depth from the reflector. For detailed descriptions of DB and EM systems see [1]. However, some issues concerning pressure profiles and deep targeting capabilities of already existing EM systems need to be further clarified and this information is outlined below.

Up to now, four major technical implementations have been described which allow non-invasive deep brain neuromodulation and can be classified as follows: (I) **multichannel** systems focusing >1000 ultrasound generating units integrated in a helmet, (II) **oligochannel** systems focusing <300 units integrated in a larger transducer which can be positioned over various brain areas, and (III) **single channel** systems with the smallest available transducer and a focus defined by the reflector characteristics. This classification is based on the number of ultrasound channels applied (for technical/physical implementations compare [2]). All systems are able to target deep or mid-level brain structures. However, systems (I) and (II) are typically limited in their capability to target superficial brain areas which is not the case for single channel systems. With single channel systems reflector properties may be constructed to target deep or superficial tissue and application of stand offs allows easy change of focal stimulation depth. Concerning sonication, two approaches exist: **monofrequency** sonication and **multifrequency** sonication based on shock wave principles. Compared to monofrequency pulses, with pulse repetition frequency typically in the ms range, multifrequency pulses are in the µs range and allow much higher peak pressures or peak intensities (compare [3]). Multifrequency pulses are currently only implemented in systems based on shock wave principles, however, multifrequency stimulation and pulse durations in the µs range could also be implemented with other systems. Achievement of high peak pressures is an important issue for human applications, since energy absorption in human skull may reach up to 85% peak intensity reductions [4]. Ham et al. report peak intensities of 0.1-5.0 W/mm^2 with monofrequency sonication, but 10 - 127 W/mm^2 with multifrequency pulses [1]. Up to now, multifrequency sonication is only implemented with single channel systems (implementation (IV): **single channel – multifrequency**).
Meanwhile, enhancement of neuronal activity at deep human brain targets has been described for all four ultrasound neuromodulation techniques. This is true for studies involving healthy human participants and clinical trials. Importantly, current evidence shows that ultrasound neuromodulation is safe and potential risks are comparable for cortical or deep stimulation (for review see [5]). According to current knowledge, effects of all technical ultrasound implementations are based on the same mechanisms of action and local stimulation effects have been proven using independent methodologies. For human use, concurrent fMRI, arterial spin labeling (ASL), or EEG have been investigated to monitor immediate or short term effects [6–8]. For assessing long term effects, more sophisticated MRI analyses such as functional connectivity analysis, diffusion tensor imaging, and MR spectroscopy [9,10], as well as EEG [11] and TMS [12] have been administered. In animal studies, invasive electrophysiological recordings [13], as well as optical and optoacoustic monitoring [14] have

been used. The following examples illustrate enhancement of neuronal activity in deep human brain areas: (I) Successful stimulation of the nucleus accumbens at around 65 mm focal depth was described for patients with substance use disorder using multichannel systems [15]. (II) With oligochannel systems, dorsal anterior and posterior cingulate cortex stimulations were performed at 60-70 mm focal depth in healthy individuals [10]. (III) Thalamus stimulation was reported for several single-channel monofrequency systems with a focal depth of approximately 55 mm, for example in patients with disorders of consciousness [16]. (IV) For single channel – multifrequency systems, enhancement of neuronal activity in the precuneus, extending to a depth of 50-60 mm, was described using Transcranial Pulse Stimulation (TPS) in patients with Alzheimer's disease [4]. TPS is the only dedicated neuromodulation system with clinical approval for neuromodulation therapy in the European Union and has already shown the clinical potential which is expected by Ham et al. from their DB system. It is also important to note that the clinical utilization of focused shockwaves (e.g., currently more than 100.000 TPS patient treatments worldwide) is more prevalent as that of Focused Ultrasound (FUS) [17,18]. A major challenge with current ultrasound neuromodulation research is the large number of sonication parameters which may be set with various sonication systems and the complexity of their interactions. Controlled variation of single key parameters (with all others kept stable) is therefore warranted for clinical research. TPS focuses on variation of pulse frequency and intensity, with increasing evidence that both are key parameters for dose-response relationships [19,20]. Importantly, TPS has a pressure profile well suited to target deep brain regions, even areas located considerably deeper than the 12 mm focus of the DB system used in the mouse model in Ham et al. [1]. Note, that deep brain stimulation in humans poses additional challenges since the human brain is larger and the skull attenuation is increased. The 50% extension of TPS peak pressure (FEHM, corresponding to FWHM in axial direction) reaches from 20 to 80 mm. At 80 mm depth, pressure measured below human skull still reaches about 4.5 MPa (Fig. 1a, compare Fig. 1 in Ham et al. [1]). Multiple studies have found larger effects when increasing pressure / intensity in vitro [20] or in vivo [21]. Therefore, it may be assumed that biological effects may be achievable even in depths > 80 mm. Due to a transversal FWHM (full width half maximum in transversal direction) of 3-4 mm and a rapid pressure rise time TPS can precisely focus in a specific deep brain region and several TPS investigations have also shown enhancement of neuronal target activity [4,9,22]. In contrast, Ham et al. did not find enhancement of neuronal activity at deep targets with their commercial EM transducer system [1]. A possible reason may be that the TPS pressure profile completely differs from the EM pressure profile. Negative pressure peaks with TPS are minor (Fig. 1b, compare Fig. 1 in [1]), whereas for EM positive and negative pressure peaks are about the same size. On a side note, exact pressure profile measurements for systems like EM or DB require a sensor size < 1.0 mm and a flat frequency response (+/-3dB) over the whole calibration range of 500kHz to 15 MHz (at least) according to the IEC61846 standard (§6). This would be achievable with a dedicated needle hydrophone or an acousto-optic fibre hydrophone as common practice in the field, but does not apply for the 113B23, PCB (Piezotronic) sensor (resonance of this sensor lies above 500kHz). This situation may impact gradients and peak pressure distributions measured (Fig. 1b in [1]) and consequently the comparison of DB with EM pressure waveforms.

Regarding deep brain activation with ultrasound neuromodulation, a further important aspect concerns neuronal network connectivity. Direct neuronal stimulation has to be differentiated from indirect neuronal stimulation mediated through network effects [5]. In analogy to electrophysiological non-invasive brain stimulation techniques like TMS, stimulation of superficial cortical areas might not only elicit direct effects on the targeted site, but also in anatomically and functionally interconnected regions [23]. Investigations in neuronal cell cultures suggest that only 3-5% of a connected network needs to be stimulated to propagate

neuronal activation [24]. Indirect effects on deep brain structures were described for TPS in Alzheimer's disease [4]. In this first clinical study with focused navigated ultrasound, no direct stimulation of hippocampal and parahippocampal areas was performed, but activation upregulation was demonstrated with functional MRI data. Hippocampal and parahippocampal activation was a consequence of stimulation of cortical nodes of a network related to memory functions. Further, an early study with healthy participants showed indirect thalamus activation as measured with functional MRI during V1 stimulation, using two sets of single-element FUS transducers [25]. A very recent study by Oh et al. demonstrated functional connectivity alterations in the anterior cingulate cortex as a consequence of stimulation of the left dorsolateral prefrontal cortex in patients with major depressive disorder with a single channel FUS system [26]. A detailed overview of clinical applications including deep brain stimulation and real-world use cases has recently been published by Matt et al. [17].

Conclusion

For all four ultrasound neuromodulation techniques (multichannel, oligochannel, single channel – monofrequency, single channel – multifrequency), comprehensive evidence exists that focal enhancement of neuronal activity in depths between 50-70 mm is possible. Besides this direct deep focal neuromodulation, there is also multiple evidence for indirect activation of deep unstimulated neurons via stimulation of connected network nodes.

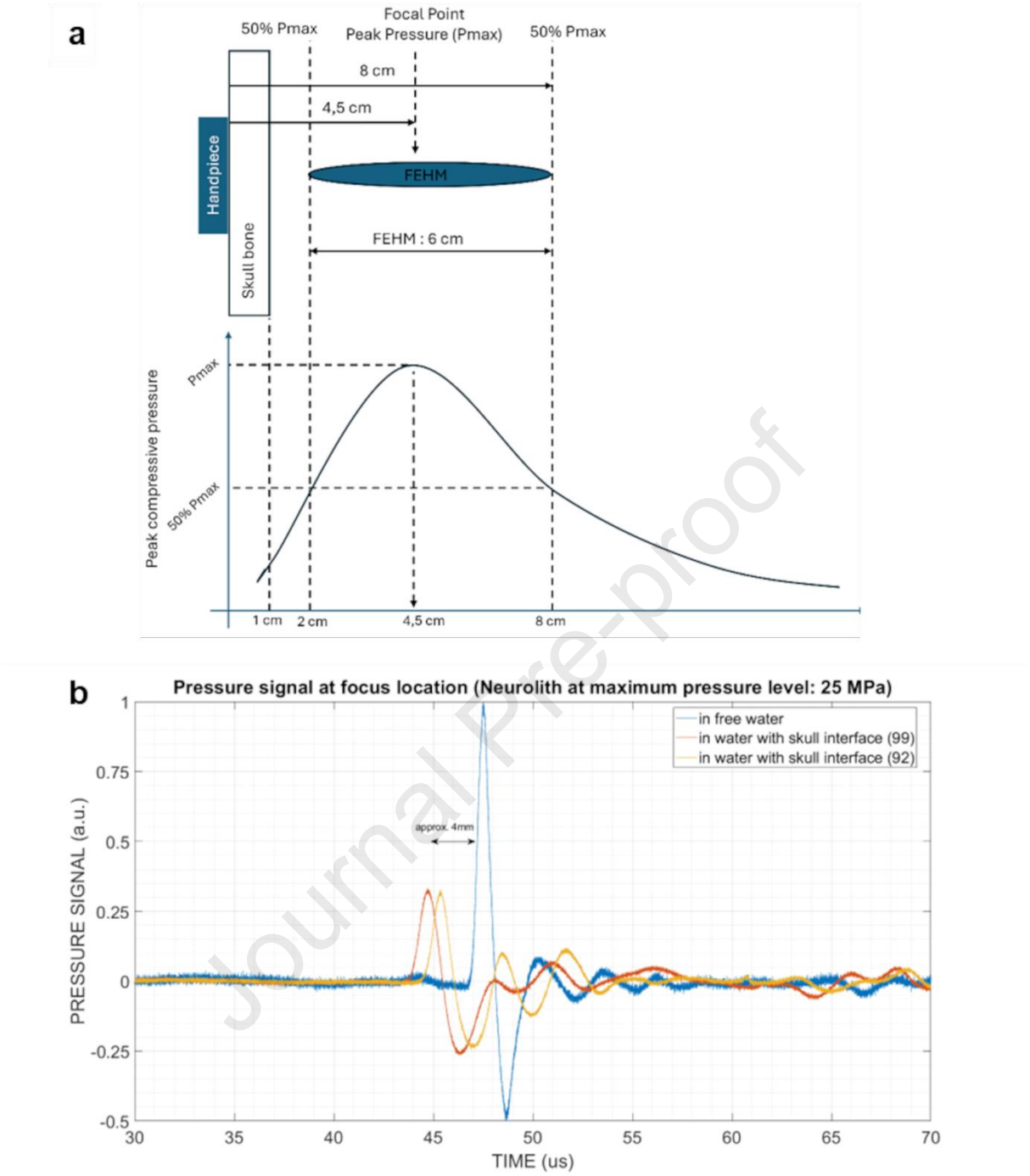

Fig. 1. Pressure Profile of Transcranial Pulse Stimulation (TPS). a) TPS peak pressure point lies at a distance of 4.5 cm from the hand piece with the FEHM (Full Extension at Half Maximum) ranging from 20 to 80 mm. At 80 mm depth, pressure measured below human skull still reaches about 4.5 MPa. b) Pressure signal is attenuated by human skull (yellow and red graphs corresponding to measurements below two human skulls).

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Conflicts of interest

RB reports financial support was provided by Herzfelder Stiftung Austria. RB reports a relationship with Storz Medical AG that includes: research support. EM declares to have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Roland Beisteiner reports financial support was provided by Herzfelder Stiftung Austria. Roland Beisteiner reports a relationship with Storz Medical AG that includes: research support. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.