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Letter to the Editor

Transcranial Pulse Stimulation (TPS) – A highly focused brain stimulation therapy with 3D navigation

We read with great interest the review "Non-invasive transcranial ultrasound stimulation for neuromodulation" by Darmani et al. (2022) which gives a valuable and comprehensive overview of the field. We agree that the novel ultrasound based brain stimulation techniques are very promising for neuroscientific research and clinical application. Specific advantages concern high spatial precision (not influenced by pathological brain conductivities) and ability to reach deep brain structures that are currently accessible only by invasive deep brain stimulation (DBS). During the last decade tremendous progress in ultrasound-based stimulation technologies has occurred, and the authors correctly point out that most studies used specific and highly focal stimulation systems (typical foci comprise 3–5 mm width and 3–5 cm length). Only few studies used diagnostic ultrasound devices with unfocused beams and continuous waves, likely to produce uncontrolled secondary stimulation maxima and local brain heating effects. However, in contrast to the authors description, the recently developed transcranial pulse stimulation (TPS) technique, which utilizes repeated ultrashort ultrasound pulses, does not belong to the class of diagnostic ultrasound devices and does not suffer from the drawbacks mentioned. The general concept of this novel brain stimulation therapy was developed about 10 years ago in Vienna, followed by an intensive search for industrial partners. An international research consortium then developed a novel method and system for brain therapy using a multidisciplinary approach. Since the TPS stimulation concept has nothing to do with diagnostic ultrasound, several years of research were required to generate a safe clinical stimulation methodology. Comprehensive pulse simulation data, laboratory experiments with animal and human skulls as well as animal and human brains, animal studies (85 rats), and SEP data in healthy subjects were acquired. In addition, the very first patient study with navigated focused ultrasound was performed with clinical benefits and neuroplastic effects documented by fMRI (Beisteiner et al., 2019). During the whole process a special focus was put on safety issues and, therefore, this publication also provided the very first report on minor transient events associated with ultrasound brain stimulation in humans (45 subjects, compare also Beisteiner and Lozano, 2020). In this context it is important to note that since TPS pulses only last 0.003 ms they cannot produce brain heating or unwanted secondary stimulation maxima. Unlike other ultrasound approaches, TPS does not apply single sinusoidal waves but sounds with a considerable portion of lower frequencies which improve skull penetration. Meanwhile clinical TPS research has also provided the first evidence of an antidepressive effect in patients with Alzheimer's disease (AD) (Matt et al., 2022a). Large double blind, crossover studies on Parkinson's disease and AD are running. Further, TPS has also provided first neuroimaging evidence that transcranial ultrasound stimulation can change structural plasticity (Popescu et al., 2021). A very recent sham controlled study also generated the first long-term data showing functional and structural connectivity effects >1 week in healthy subjects (Matt et al., 2022b).

TPS meanwhile is the most widely spread ultrasound based focal neuromodulation technique used in more than 60 clinical and research centers worldwide. Clinical experience includes more than 6000 applications without occurrence of serious adverse events. We agree with Darmani and colleagues that non-invasive transcranial ultrasound stimulation for neuromodulation is very promising to further establish brain stimulation as an effective add-on therapy. Of course, research focusing on how and where these novel techniques provide the largest clinical benefit yet have to be performed. However, the good news for patients is that they can continue all state of the art treatments and get an additional therapeutic chance.

Declaration of Competing Interest

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M.H. is an inventor of patents held by NIH for an immunotoxin for the treatment of focal movement disorders and the H-coil for magnetic stimulation; in relation to the latter, he has received license fee payments from the NIH (from Brainsway). He is on the Medical Advisory Boards of CALA Health and Brainsway (both unpaid positions). He is on the Editorial Board of approximately 15 journals and receives royalties and/or honoraria from publishing from Cambridge University Press, Oxford University Press, Springer, Wiley, Wolters Kluwer, and Elsevier. He has research grants from Medtronic, Inc. for a study of DBS for dystonia and CALA Health for studies of a device to suppress tremor.

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