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# Ultrasound Neuromodulation as a New Brain Therapy

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Abstract and Figures

Within the last decade, ultrasound has been "rediscovered" as a technique for brain therapies. Modern technologies allow focusing ultrasound through the human skull for highly focal tissue ablation, clinical neuromodulatory brain stimulation, and targeted focal blood-brain-barrier opening. This article gives an overview on the state-of-the-art of the most recent application: ultrasound neuromodulation as a new brain therapy. Although research centers have existed for decades, the first treatment centers were not established until 2020, and clinical applications are spreading rapidly.

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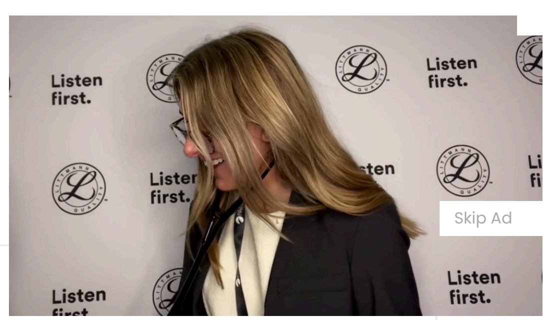


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# Ultrasound Neuromodulation as a New Brain Therapy

*Roland Beisteiner,* Mark Hallett, and Andres M. Lozano*

**Within the last decade, ultrasound has been "rediscovered" as a technique for brain therapies. Modern technologies allow focusing ultrasound through the human skull for highly focal tissue ablation, clinical neuromodulatory brain stimulation, and targeted focal blood-brain-barrier opening. This article gives an overview on the state-of-the-art of the most recent application: ultrasound neuromodulation as a new brain therapy. Although research centers have existed for decades, the first treatment centers were not established until 2020, and clinical applications are spreading rapidly.**

## 1. Introduction

Within the last decade, ultrasound has been "rediscovered" as a technique for brain therapies. Notably, the very first medical applications of ultrasound were neurological applications: Pohlmann et al.[1] tried to treat patients with neuralgia, and Dussik et al.[2] generated the first ultrasound image, showing the lateral ventricles of the human brain. Modern technologies allow focusing ultrasound through the human skull and enable non-invasive stimulation or ablation of brain tissue. Clinical neuroscientific studies have shown that: a) highly focal tissue ablation (e.g., tremor therapy); b) clinical neuromodulatory brain stimulation (e.g., Alzheimer's therapy); and c) targeted focal blood-brain-barrier opening (e.g., focal drug transfer) are possible. Meanwhile, ultrasound surgery and, just recently, ultrasound neuromodulation have entered routine clinical therapy.[3,4] The rapidly ongoing methodological and clinic progress opens completely novel perspe tives for ultrasound brain therapy. This important since brain diseases are one the most urgent problems in our rapid ageing society. Effective medications a often missing (e.g., for dementias) ar application of surgery is limited due invasiveness, particularly in the elderly. light of increasing therapeutic applicatic of ultrasound neuromodulation and ther peutic patient requests, this article focus on ultrasound neuromodulation as a ne brain therapy. Although research centers have existed f decades, the first treatment centers were established in 2020 ar currently no detailed overview over clinically applicable technol gies, current therapeutic results, and therapeutic benefits cor pared to electromagnetic therapies exist.

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## 2. Methodology of Clinical Ultrasound Neuromodulation

Three technical approaches have been used to modulate huma brain activity. The first approach comprises standard diagnost systems built for Transcranial Doppler Sonography to monit and diagnose the intracerebral blood flow situation. Althoug they have a limited field of view, they cannot be focused to small brain area. The second approach is highly focused system which can target stimulation to very small brain areas. The thi approach is highly focused and individually navigated system which allow us to precisely target individual brain areas on i dividual magenetic resonance (MR) images. Since every bra is different and pathologies may result in gross morphologic brain changes, precise targeting capabilities are essential. Ther fore, highly focused navigated systems are clearly state-of-the-a for clinical ultrasound neuromodulation.

For highly focused ultrasound systems two different class exist. The first class builds on diagnostic ultrasound and us sinus tones (single ultrasound frequencies) in the range of se eral hundred kilohertz. This approach is described as Focuse Ultrasound (FUS). Typically, FUS sinus tones are presented a pulsed mode, which means short trains of ultrasound (e.g 100 ms) are followed by silence (e.g., 300 ms). The relationsh between the ultrasound train and the following pause before th next ultrasound train defines the duty cycle (here 25%). In th literature an extraordinary variability in sonication schemes h been described, including a blocked presentation of duty cycl which may then be paused for a longer time (seconds) and thu generate longer second order stimulation pulses (e.g.,[5]). F neuromodulatory effects, such sonication patterns are used ov several minutes. Meanwhile, various FUS systems are in huma

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... The tFUS renaissance has also spurred exciting developments in human neuroscience research 21 , increasing its potential for addressing clinical challenges [21] [22] [23] . In addressing the medical challenge of disorders of consciousness (DOC), Cain et al. applied low-intensity focused ultrasound to the central thalamus in a cohort of DOC patients 24 . ...

... The data were z-scored with respect to the 200 ms pre-stimulus baseline. N200 powers were computed by applying timefrequency Morlet waveform power transformation to the 100 to 250 ms post-stimulus window for theta (4)(5)(6)(7)(8), alpha (8 -12 Hz), beta (12)(13)(14)(15)(16)(17)(18)(19)(20)(21) (22) (23)(24)(25)(26)(27)(28)(29)(30), and low gamma (30-40 Hz) frequencies (Fig. 3). Linear mixed-effect models were fitted to N200 powers as a function of experimental condition (Eq. ...

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... Two classes of technologies are currently available for navigated focal stimulation, low-intensity transcranial focused ultrasound (e.g., tFUS, LIFUS) and transcranial pulse stimulation (TPS). While tFUS is administered in intermittent trains of ultrasound pulses using sinus tones, TPS applies ultrashort (3 µs) pressure pulses with a range of different frequencies which are repeated at 1 to 8 Hz (for review see Beisteiner et al., 2023) . Both techniques result in an elongated elliptical ultrasound beam with an axial resolution of approximately 4 cm and a transversal resolution of approximately 4 mm full width at half maximum for typical carrier frequencies of 500 kHz for tFUS and 250 kHz for TPS (Beisteiner et al., 2019;Truong et al., 2022). ...

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... tFUS is an emerging, non-invasive neuromodulation tool for deep brain stimulation that has shown promise in treating various neurological and psychiatric conditions [14][15] [16] . Following its FDA approval for Parkinson's disease and essential tremor, tFUS has seen significant advancements in clinical validation [17]. There is an increasing urgency to optimize tFUS therapeutic applications through expanding research. ...

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... TPS may play an important role in the restoration of brain function in individuals with CNS diseases (35). Application of ultrasound to the brain is a revolutionary therapeutic approach for patients with neuropsychiatric symptoms (37, 38). Since transcranial pulse stimulation (TPS) is a relatively new noninvasive brain stimulation (NIBS) technology, only four studies thus far have been conducted in clinical populations. ...

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Current state of clinical ultrasound neuromodulation

June 2024 · Frontiers in Neuroscience

Eva Matt · Sonja Radjenovic · Michael Mitterwallner · Roland Beisteiner

Unmatched by other non-invasive brain stimulation techniques, transcranial ultrasound (TUS) offers highly focal stimulation not only on the cortical surface but also in deep brain structures. These unique attributes are invaluable in both basic and clinical research and might open new avenues for treating neurological and psychiatric diseases. Here, we provide a concise overview of the expanding ... [Show full abstract]

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Safety of Clinical Ultrasound Neuromodulation

September 2022 · Brain Sciences

Sonja Radjenovic · Gregor Dörl · Martin Gaal · Roland Beisteiner

Transcranial ultrasound holds much potential as a safe, non-invasive modality for navigated neuromodulation, with low-intensity focused ultrasound (FUS) and transcranial pulse stimulation (TPS) representing the two main modalities. While neuroscientific and preclinical applications have received much interest, clinical applications are still relatively scarce. For safety considerations, the ... [Show full abstract]

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Human Ultrasound Neuromodulation: State of the Art

February 2022 · Brain Sciences

Roland Beisteiner

The first human applications of ultrasound in medicine date back to 1939, when Reimar Pohlmann (Berlin, Germany) published data on therapy of neuralgia with ultrasound [...]

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