

Treating the brain at the speed of sound

A B S T R A C T

Keywords:

Ultrasound brain stimulation

One of the most important public issues in our rapidly ageing society are brain disorders and neurodegenerative diseases. Effective therapies are limited and therefore costs for public health systems rapidly increase in this sector. However, recently the first clinical evidence for a new class of therapies has emerged - ultrasound for the brain. With the first clinical data on ultrasound brain activation just now published, three fascinating options are available to revolutionize non-invasive brain therapy. All three ultrasound therapies currently receive widespread attention from patients and doctors.

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One of the most important public issues in our rapidly ageing society are brain disorders and neurodegenerative diseases. Effective therapies are limited and therefore costs for public health systems rapidly increase in this sector. However, recently the first clinical evidence for a new class of therapies has emerged – ultrasound for the brain. With the first clinical data on ultrasound brain activation just now published, three fascinating options are available to revolutionize non-invasive brain therapy. All three ultrasound therapies currently receive widespread attention from patients and doctors (see Fig. 1).

The first concerns non-invasive and highly targeted surgery, where high intensity focused ultrasound (HIFU) beams destruct pathologically active axons and neurons. In a seminal study of deep brain surgery of the thalamus (thalamotomy) for medically resistant essential tremor, HIFU has been shown to produce clear and sustained benefits [1]. Meanwhile further clinical studies have been done in Non-Essential Tremor Syndromes, Parkinson's disease and Obsessive Compulsive Disorder. In addition, promising preclinical studies exist for Stroke, Tumor ablation, Epilepsy and surgery of the brain ventricles.

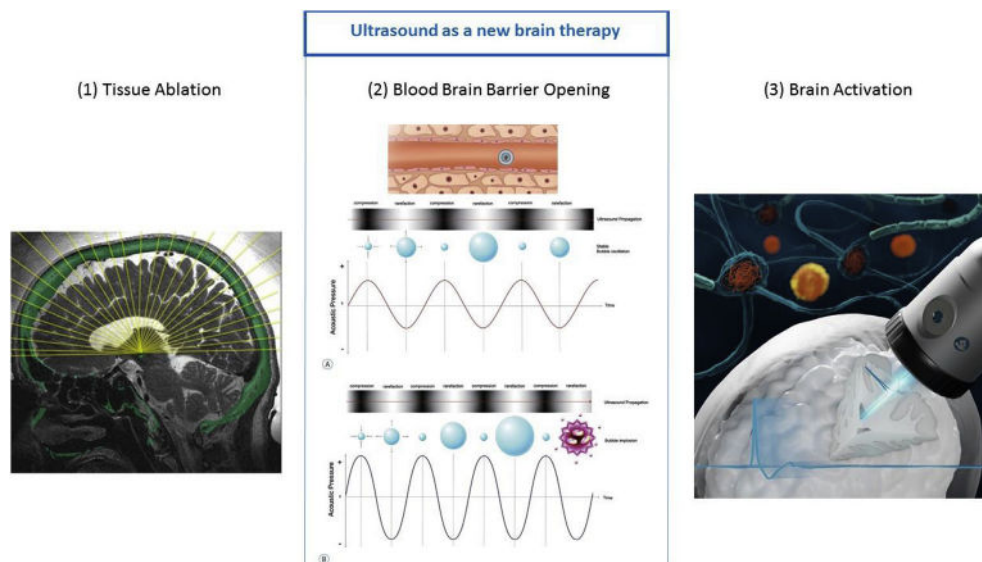


Fig. 1. 3 new therapeutic options may revolutionize brain therapy. (1) Multiple sources of Ultrasound focused to specific brain targets for lesioning. (2) Microbubbles are used to focally open the BBB with ultrasound. (3) A single ultrasound source is used for focal brain activation – superficially or deep in the brain.

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The second avenue concerns targeted local drug delivery or local gene therapy by focal opening of the restrictive blood-brain barrier. As a means of brain protection, the blood-brain barrier hinders a lot of substances and therapeutic drugs from entering the brain. Recent patient studies have now shown that focal access to diseased brain tissue via focal blood-brain barrier opening is possible. This concept is feasible in Alzheimer's [2], brain tumor and amyotrophic lateral sclerosis patients [3]. Preclinical studies exist for Parkinson's disease, Depression and Epilepsy. Due to the huge clinical potential, a large body of methodological work currently investigates how to optimize these focal drug and gene transfers. Future clinical options include stem cell transfers, activation of neurogenesis, immune system activation, neuroprotection, ablation options and even modulation of brain activity.

Important inroads are also being made in the third option, direct non-invasive modulation of neural activity without opening of the blood-brain barrier. A first patient study just published shows persistent activation of memory networks in Alzheimer's patients with ultrasound [4]. In this study a new pulsed ultrasound technique (Transcranial Pulse Stimulation, TPS) was used, which is already clinically approved (CE certification). Although clinical brain stimulation has been pursued over decades with electromagnetic technologies, limitations exist for pathological brains and for deep brain stimulation [5]. It is a major clinical progress that ultrasound and TPS now allow secure targeting (even with dramatic intracranial conductivity changes) and focal access to deep brain areas. Given that therapeutic deep brain stimulation currently requires surgery and electrode implantations, we are now on the verge of a first non-invasive Deep Brain Stimulation (DBS) approach. Most likely, ultrasound neuromodulation rests on an initial change of cell membrane permeability [6]. This causes a cascade of transmitter, humoral factor and cell activity changes with longterm neuroplastic effects. In the recent TPS study, the procedure was well tolerated and after 2 weeks of treatment, memory performance improved for up to 3 months.

The novel concepts for ultrasound brain therapy have been developed in a fascinating rally over the last decade. They have the potential to revolutionize brain therapy by using focal beams for non-invasive tissue destruction, non-invasive transmission of drugs/genes and therapeutic modulation of pathological brain networks with clinical long-term effects.

Declaration of competing interest

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