Brain Stimulation 13 (2020) 1087–1088

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Treating the brain at the speed of sound

Keywords:
Ultrasound brain stimulation

A B S T R A C T

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.

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.

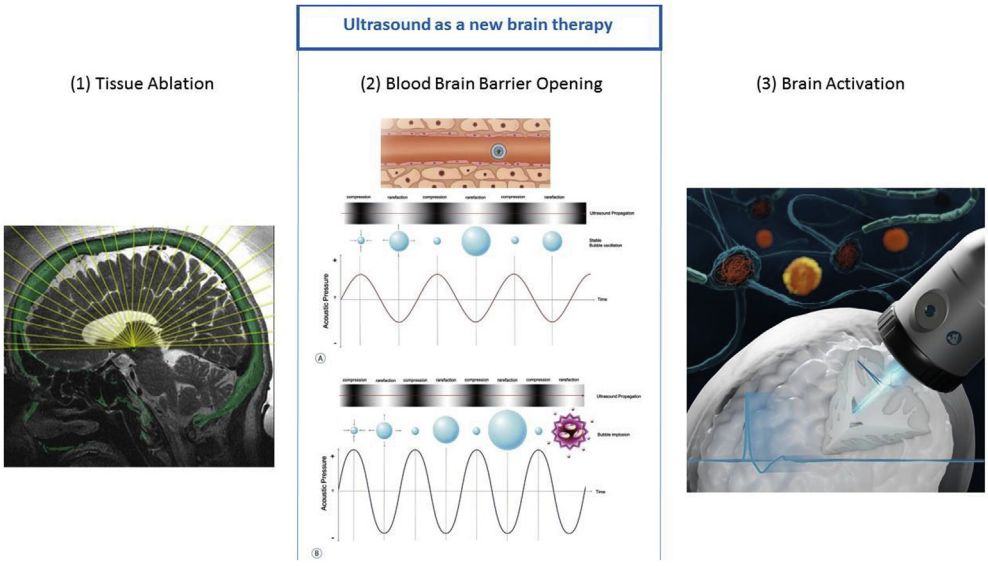

Fig. 1. 3 new therapeutic options may revolutionize brain therapy. (1) Multiple sources of Ultrasound focused to specific brain targets for lesioning. (2) Microbubbles are used to focally open the BBB with ultrasound. (3) A single ultrasound source is used for focal brain activation – superficially or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

https://doi.org/10.1016/j.brs.2020.04.020

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 amyothrophic 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

Part of the original data referenced was supported by Storz Medical Inc. to RB. AML is consultant to Medtronic, Boston Scientific, Abbott, Insightec and Functional Neuromodulation.

References

[1] Elias WJ, Lipsman N, Ondo WG, Ghanouni P, Kim YG, Lee W, Schwartz M, Hynynen K, Lozano AM, Shah BB, Huss D, Dallapiazza RF, Gwinn R, Witt J, Ro S, Eisenberg HM, Fishman PS, Gandhi D, Halpern CH, Chuang R, Butts Pauly K, Tierney TS, Hayes MT, Cosgrove GR, Yamaguchi T, Abe K, Taira T, Chang JW. A randomized trial of focused ultrasound thalamotomy for essential tremor. N Engl J Med 2016 Aug 25;375(8):730–9. https://doi.org/10.1056/NEJMoa1600159.

[2] Lipsman N, Meng Y, Bethune AJ, Huang Y, Lam B, Masellis M, Herrmann N, Heyn C, Aubert I, Boutet A, Smith GS, Hynynen K, Black SE. Blood-brain barrier opening in Alzheimer's disease using MR-guided focused ultrasound. Nat Commun 2018 Jul 25;9(1):2336. https://doi.org/10.1038/s41467-018-04529-6.

[3] Abrahao A, Meng Y, Llinas M, Huang Y, Hamani C, Mainprize T, Aubert I, Heyn C, Black SE, Hynynen K, Lipsman N, Zinman L. First-in-human trial of blood-brain barrier opening in amyotrophic lateral sclerosis using MR-guided focused ultrasound. Nat Commun 2019 Sep 26;10(1):4373. https://doi.org/10.1038/s41467-019-12426-9.

[4] Beisteiner R, Matt E, Fan C, Baldysiak H, Schönfeld M, Philippi Novak T, Amini A, Aslan T, Reinecke R, Lehrner J, Weber A, Reime U, Goldenstedt C, Marlinghaus E, Hallett M, Lohse-Busch H. Transcranial Pulse Stimulation with Ultrasound in Alzheimer's disease – a new navigated focal brain therapy. Adv Sci 2019, Dec 23;7(3):1902583. https://doi.org/10.1002/advs.201902583.

[5] Spagnolo PA, Wang H, Srivanitchapoom P, Schwandt M, Heilig M, Hallett M. Lack of target engagement following low-frequency deep transcranial magnetic stimulation of the anterior insula. Neuromodulation 2019 Dec;22(8):877–83. https://doi.org/10.1111/ner.12875. Epub 2018 Oct 29.

[6] Tyler WJ, Lani SW, Hwang GM. Ultrasonic modulation of neural circuit activity. Curr Opin Neurobiol 2018 Jun;50:222–31. https://doi.org/10.1016/j.conb.2018.04.011. Epub 2018 Apr 16. Review.

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21 April 2020
Available online 6 May 2020