

quite modest. Indeed, these effects are more than an order of magnitude lower than the effect of the *APOE*  $\epsilon 4$  allele on AD risk. Further studies will be needed to clarify the functional basis of these associations. Only after this objective is accomplished can we be sure that we have identified novel AD risk genes. Identification of novel AD risk genes is necessary if we are to improve our capacity for early prediction and, hopefully, prevention of this devastating disease.

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#### Competing interests

The authors declare no competing interests.

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#### PAIN

## Noninvasive functional neurosurgery using ultrasound

William J. Tyler, Yusuf Tufail and Sandipan Pati

**Ultrasound-based technologies are emerging as promising noninvasive approaches to treat brain disorders. Researchers in Switzerland have shown that chronic pain can be alleviated through thermal ablation of thalamic tissue by high-intensity focused ultrasound.**

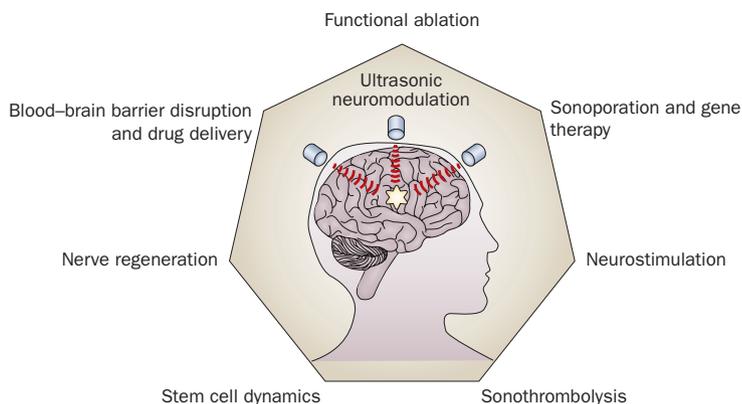
Burgeoning neurotechnologies are providing clinicians with the means to meet one of the greatest challenges in modern medicine—the effective treatment of brain disorders. The neurotechnology community is faced with the task of developing medical interventions that balance the level of necessary invasiveness with therapeutic efficacy. Deep brain stimulation, for example, has been shown to be remarkably effective in treating neurological disorders such as Parkinson disease, but it necessitates the surgical implantation of electrodes and microcontroller devices. Transcranial magnetic stimulation is non-invasive, but is hampered by poor spatial resolution and brain penetration power, and its robustness in treating psychiatric disorders such as depression remains hotly debated. Gamma knife radiosurgery is another noninvasive approach that has been used to treat various brain diseases, but concerns have been raised regarding the adverse effects of its ionizing radiation on tissues surrounding the treatment zones. More than eight decades of basic science and clinical research efforts have culminated in the emergence of ultrasound-based technologies that could provide new and improved noninvasive standards of care in neurological and psychiatric medicine. A phase I trial conducted by Ernst Martin and colleagues in Zurich, Switzerland has illustrated the efficacy of one such approach in patients with chronic pain.<sup>1</sup>

Ultrasound is routinely used for many types of diagnostic imaging, but has been largely overlooked in favor of other therapeutic modalities for the clinical management of CNS disorders. In 1929, Edmund Harvey Newton first demonstrated that ultrasound has an effect on neural tissues by showing that it was capable of stimulating nerve and muscle.<sup>2</sup> Several decades later, William Fry and colleagues demonstrated the production of functional lesions in the mammalian brain through ultrasound, in

a technique that they later termed ‘neurosonicsurgery.’<sup>3</sup> By the late 1950s, Fry and his colleagues were implementing high-intensity ultrasound to treat patients with movement disorders.<sup>5,6</sup> Despite some preliminary success, ultrasound as a neurotherapeutic tool was mostly discounted by the medical community at the time, since the treatment procedures required major craniotomy to enable focusing of ultrasound through the skull.

Technological breakthroughs over the past few years have made it possible to transmit and focus ultrasound through the intact human skull. To enable non-invasive treatment of brain tissues with ultrasound, Kullervo Hynynen and colleagues have refined an image-guided technique known as MRI-guided focused ultrasound (MRgFUS), which is presently used to thermally ablate uterine fibroids by means of high-intensity focused ultrasound (HIFU).<sup>7,8</sup> In the general MRgFUS approach to treating brain tissues with ultrasound, a CT scan is first used to generate information about the density of skull bone. Algorithms are then used to predict the location of ultrasound beams by correcting for distortions and aberrations produced by the transcranial transmission of ultrasound. To maximize the targeting accuracy, ultrasound transducers are arranged in a hemispheric phased array that transmits ultrasound to targeted brain regions, while MRI-based thermometry continuously provides feedback of ultrasound beam location and focusing in a closed-loop system.

The findings from a phase I clinical study published in *Annals of Neurology* represent a major step forward in bringing ultrasound-based treatments of brain diseases to fruition. Martin and colleagues used transcranial MRI-guided HIFU (tcMRgHIFU) to perform lesions of the central lateral thalamic nuclei in nine patients with chronic neuropathic pain.<sup>1</sup> These interventions relied on the capacity of



**Figure 1** | Potential applications of ultrasonic neuromodulation for the noninvasive treatment of brain disorders. Through both thermal and nonthermal (mechanical) mechanisms, ultrasound has been shown to exert numerous bioeffects on brain tissues that could provide a basis for noninvasive therapies for neurological and psychiatric disorders.

tcMRgHIFU to heat brain tissues to temperatures  $>53^{\circ}\text{C}$  to achieve thermal ablations through multiple, repeated sonication events. All patients receiving the outpatient tcMRgHIFU procedure remained awake and responsive during the entire neurosurgical intervention, which resulted in thalamotomies  $\approx 4$  mm in diameter. With respect to clinical outcomes, the patients reported a mean 68% reduction in pain 2 days after the procedure. The treatment was well tolerated in all cases, and no adverse effects or neurological impairments were reported. The observations of Martin *et al.* provide the first demonstration of a noninvasive neurosurgical intervention employing MRgFUS, which could open up new possibilities for the treatment of other neurological disorders.

The tcMRgHIFU approach possesses several clinical advantages over other noninvasive neurosurgical procedures such as gamma knife radiosurgery. The ablation produced by tcMRgHIFU is of thermal origin, which produces instant cell death through coagulative necrosis, in contrast to lesions produced by ionizing radiation, which typically require days to produce cell death. The speed of lesion production by tcMRgHIFU could prove to be particularly beneficial in treating diseases

such as aggressively proliferating tumors. In addition, the demarcation of treatment margins in tcMRgHIFU is tighter than that achieved using ionizing radiation, which could reduce the risk of negatively affecting surrounding healthy tissues. On the basis of these realizations, other ongoing clinical trials are evaluating the use of tcMRgHIFU in the treatment of pervasive brain diseases such as glioblastoma.

After nearly a century of research and development, ultrasound is finally beginning to deliver on its promise as a therapeutic modality for the noninvasive treatment of brain diseases. Ultrasound has been shown not only to provide a mode of conducting thermal ablations, as demonstrated by Martin *et al.*,<sup>1</sup> but also to exert nonthermal, mechanical effects on brain tissues that could provide positive therapeutic outcomes. Possible applications of these latter effects include sonothrombolysis of brain blood clots, transient focal opening of the blood-brain barrier for local drug delivery, gene transduction of neurons through sonoporation, promotion of nerve regeneration, promotion of cell proliferation, and stimulation of action potentials and synaptic transmission in brain circuits (Figure 1).<sup>9</sup> With further research and clinical evaluation,

ultrasound has the potential to revolutionize neurological and psychiatric medicine by providing noninvasive treatments for brain disorders.

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#### Competing interests

W. J. Tyler declares an association with the following company: SynSonix. See the article online for full details of the relationship. Y. Tufail and S. Pati declare no competing interests.

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