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HOT TOPICS

Reaching for the unreachable: low intensity focused ultrasound for non-invasive deep brain stimulation

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Low intensity focused ultrasound (LIFU) is poised to become a paradigm-shifting technology with the potential to deliver non-invasive, reversible, and focal deep brain stimulation. Best understood as a type of transcranial ultrasound, LIFU uses acoustic energy to modulate regional brain activity, reaching deep and subcortical brain regions implicated in psychiatric disorders at high spatial precision [1]. In contrast to high intensity focused ultrasound, which is thermally ablative, LIFU appears to reversibly modulate neural activity, presumably without injury.

There is an emerging literature describing potential mechanisms of LIFU. One possibility is thermal (i.e., the mechanism underlying ablative high intensity focused ultrasound), yet LIFU delivers insufficient energy to meaningfully raise tissue temperature. Other mechanisms have been proposed, including opening of mechanosensitive ion channels, and even microtubule resonance (for the interested reader, see [2]). There are also growing indications of the promise of this technology. Nonhuman primate work demonstrates that LIFU can reversibly suppress amygdala and anterior cingulate activity, with effects lasting up to several hours after sonication [3]. In humans, LIFU has been shown to attenuate amplitudes of somatosensory-evoked potentials when targeting the somatosensory cortex [4], and modulate pain perception when applied to the subcortical thalamus [5] in healthy participants. Few studies have evaluated LIFU in patients, though an initial report indicated that thalamic-targeted LIFU may improve symptoms in patients with disorders of consciousness [6].

Like any neuromodulation, there are important technical elements to understand. LIFU uses a piezoelectric transducer that converts electrical signal into an acoustic beam, typically focused to a small ellipsis a few millimeters wide and centimeters long. A duty cycle describes the time in a cycle the machine is on and the total energy delivered is expressed in units of intensity, typically constrained by the US Food and Drug Administration's upper limit of safety for diagnostic ultrasound. Furthermore, because LIFU is delivered through the skull, individual variability (e.g., skull density and composition) may impact accurate administration.

As with any new field, there is no shortage of important questions. First and foremost, is LIFU safe? As mentioned above, safety standards were developed before the current technology existed, underscoring the need to carefully establish safe use. Since LIFU uses acoustic (i.e., mechanical) energy, and many deep brain regions are adjacent to important components of the cerebral vasculature (e.g., circle of Willis), very cautious implementation is warranted. To date, LIFU appears to disrupt neural targets, though the directionality of effects (i.e., inhibitory or excitatory) is yet unknown. Whether this technology reliably modulates deep brain regions is an active area of inquiry; if successful, LIFU will open an entirely novel way to evaluate neurophysiological and clinical effects from direct target engagement.

In pursuit of answers, we launched a first-in-patient study to apply a controlled use of LIFU to modulate the amygdala in depressed patients (NCT05147142), and the first patient received LIFU in October 2021. Caveats aside, LIFU is poised to be a transformative technology in neuropsychiatric research and treatment. For the first time, non-invasive, reversible deep brain stimulation may be within our reach.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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