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HOT TOPICS

Transcranial focused ultrasound (tFUS): a promising noninvasive deep brain stimulation approach for pain

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Pain is a complex experience that involves sensory, emotional, and motivational dimensions. There are several cortical and subcortical brain structures that contribute to this complexity, including the somatosensory cortex, thalamus, insula, amygdala, and prefrontal cortex. Presently, the most reliable anti-pain effects are elicited via opioids binding at nociception structures to elicit reductions in pain. With the proliferation of opioids, and their serious side effects and potential for abuse, alternative interventions like noninvasive brain stimulation targeting these pain-related brain regions could provide an alternative solution [1].

Two common noninvasive neurostimulation approaches for pain are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). TMS, which is Food and Drug Administration (FDA) approved for treating depression, induces reliable effects on the cortex, and produces anti-pain effects via downstream release of endogenous opioids [2]. tDCS is a low-amplitude electrical stimulation modality demonstrating a mild analgesic effect. Many of the pain network structures are found deep within the brain, inaccessible by TMS or tDCS (Fig. 1). Therefore, there is a need for a non-invasive, deep neuromodulation approach to access pain associated brain structures.

Transcranial focused ultrasound (tFUS) has emerged as a promising new technology that is both noninvasive and deep in its bioeffects [3]. tFUS utilizes piezoelectric transducers generating ultrasonic waves that summate deep in the brain. These ultrasonic forces have a deeper penetration range and more focal resolution than TMS (Depth: tFUS $\approx$ 1–12 cm, TMS $\approx$ 1–4 cm; Focality: tFUS $<$ 1 cm, TMS $<$ 3 cm). tFUS, when delivered at a high intensity (1000 W), ultrasound causes tissue heating (thermoablation), and thus permanent, irreversible lesions, which has clinical utility. At lower intensities (<50 W), ultrasound allows for stimulation of tissue without heating, which can be used for excitatory or inhibitory neuromodulation. Prior research has established parameter safety limits for tFUS in single-sessions, which are further reinforced by guidelines set forth by the US FDA. However, further preclinical and human safety trials are needed to establish long-term tFUS safety, in light of optimization needed to improve efficacy [4], including increasing sonication time (maximum safe session length), cumulative effects (maximum safe number of repeated sessions), and power (maximum safe wattage).

Since establishing tFUS safety, its potential to modulate deep brain structures noninvasively has spurred increased research in how it may impact brain function in pain. Legon and colleagues demonstrated that tFUS of the thalamus inhibits sensory evoked potentials (SEPs) in healthy individuals [5]. Badran and colleagues recently reported that MRI-guided tFUS focused on the thalamus produced antinociceptive effects in healthy subjects [6]. Both reports shed new light on the safety and target engagement of tFUS in deep brain structures. In order to move tFUS forward as a potential pain intervention, several integral components of the technology still need refinement, including parametric optimization (fundamental frequency, intensity), dose optimization (duration of sonication), and deep brain target selection (insula, amygdala, thalamus). If optimized, tFUS has the potential to not only help further understand the dynamic interconnected nature of deep brain structures in the processing of pain, but ultimately move towards becoming an exciting new treatment for pain disorders.

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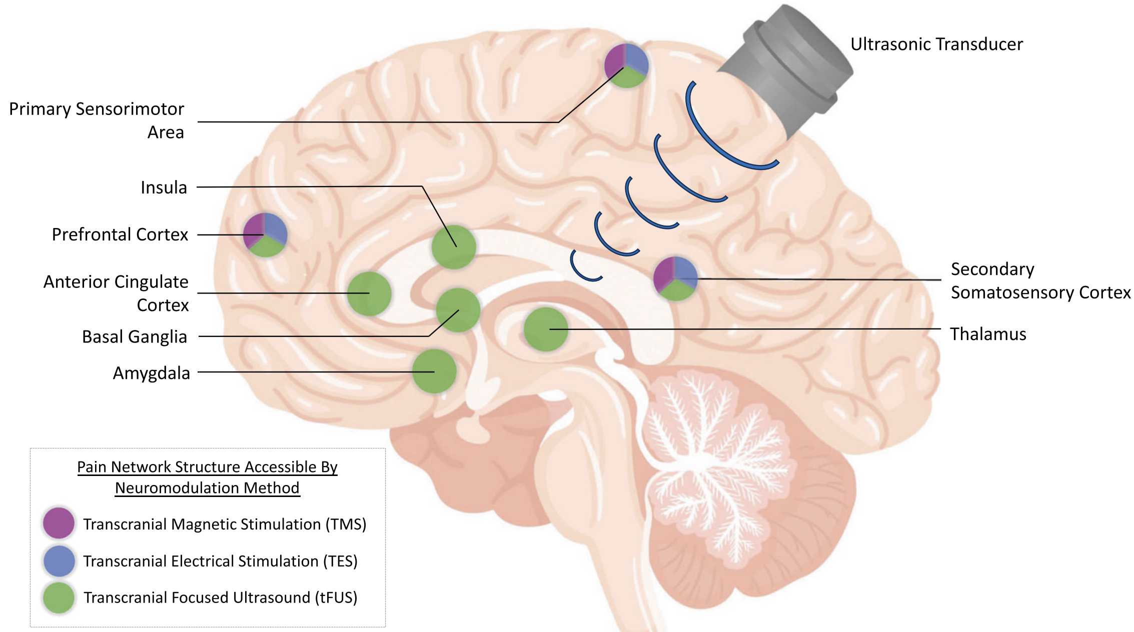

Fig. 1 Ultrasound can modulate deep brain structures associated with pain. The pain network is a series of connected cortical (primary sensorimotor area, secondary somatosensory cortex, and prefrontal cortex) and deep (insula, anterior cingulate cortex, basal ganglia, amygdala, thalamus) brain structures. Commonly used neuromodulation techniques like transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are capable of modulating only cortical areas as potential anti-pain approaches. Transcranial focused ultrasound (tFUS) however, can target both cortical and deep brain structures in the pain network, opening new areas of research that otherwise was only accessible through conventional surgical deep brain stimulation approaches. tFUS, which uses an ultrasonic transducer coupled to the scalp, is an exciting new technology that has the potential to change the trajectory of neuromodulatory interventions for pain and make a profound impact on the way we manage pain in the future.

REFERENCES

1. Xiong HY, Zheng JJ, Wang XQ. Non-invasive brain stimulation for chronic pain: state of the art and future directions. Front Mol Neurosci. 2022;15:888716.
2. Taylor JJ, Borckardt JJ, George MS. Endogenous opioids mediate left dorsolateral prefrontal cortex rTMS-induced analgesia. Pain. 2012;153:1219–25.
3. di Biase L, Falato E, Di Lazzaro V. Transcranial focused ultrasound (tFUS) and transcranial unfocused ultrasound (tUS) neuromodulation: from theoretical principles to stimulation practices. Front Neurol. 2019;10:549.
4. Sarica C, Nankoo JF, Fomenko A, Grippe TC, Yamamoto K, Samuel N, et al. Human studies of transcranial ultrasound neuromodulation: a systematic review of effectiveness and safety. Brain Stimul. 2022;15:737–46.
5. Legon W, Ai L, Bansal P, Mueller JK. Neuromodulation with single-element transcranial focused ultrasound in human thalamus. Hum Brain Mapp. 2018;39:1995–2006.
6. Badran BW, Caulfield KA, Stomberg-Firestein S, Summers PM, Dowdle LT, Savoca M, et al. Sonication of the anterior thalamus with MRI-Guided transcranial focused ultrasound (tFUS) alters pain thresholds in healthy adults: a double-blind, sham-controlled study. Brain Stimul. 2020;13:1805–12.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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