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HOT TOPICS

Potential applications of temporal interference deep brain stimulation for the treatment of transdiagnostic conditions in psychiatry

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Neuromodulation affords numerous possibilities for alleviating suffering related to psychiatric disorders, from enhancing attentional control and motivation to inhibiting exaggerated fear responses and compulsions. To date, surgically-implanted deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS) are the most widely-studied approaches. Both have significant limitations. DBS is highly costly and invasive, and surgical implantation of electrodes may have adverse effects (e.g., brain hemorrhage during surgery, infection). In contrast, TMS is a non-invasive stimulation technique that involves the application of magnetic field pulses delivered by electromagnetic coils placed against the scalp. These coils deliver a current that excites cortical electrical activity. However, TMS has limited focality, in that only surface brain structures may be safely targeted (~ 0.5–1 cm). As such, TMS can only influence deeper structures via their connectivity to superficial areas, which precludes selective targeting of key subcortical structures (e.g., amygdala, striatum) implicated in transdiagnostic conditions. This places significant limitations on TMS as a tool for studying psychiatric pathophysiology as well as a treatment modality.

Recently, temporal interference (TI) has emerged as an alternative, non-invasive deep brain stimulation method [1] that is proposed to directly stimulate regions at depth using electrodes placed at the scalp. The premise of TI is that neurons do not respond to high-frequency electrical fields due to intrinsic low-pass filtering of these signals at the neuronal membrane [2, 3]. However, when two different high-frequency fields are applied, they create a difference low-frequency "envelope" where the two fields overlap, which is within the physiological range of brain activity (Fig. 1). The properties of the waveforms and the configuration of electrodes determine the location and size of the stimulation target, which can be placed anywhere on the scalp. Emerging data suggest that TI may be used to target deep brain structures without perturbing the cortex; for example, TI has been used to selectively modulate hippocampal activity [4]. Though more research is needed, the safety profile of TI is promising, with mild (e.g., fatigue, headache) adverse reactions reported to date [5, 6]. Additionally, participants exhibit little awareness of TI, making it ideal for experimental blinding.

As such, TI offers exciting possibilities as both a tool for understanding pathophysiology and as a potential treatment. For example, TI could be used for causal manipulations of brain structures whose function in humans has largely been inferred through triangulation of preclinical experimentation and correlative neuroimaging data. It has possibilities for effectively "mapping" circuits; multiple stimulator pairs can be utilized to target multiple regions in TI, exploring connectivity through modulation of regions within a single pathway. It has numerous potential applications for intervention. Inhibitory TI of the amygdala could be used to inhibit exaggerated fear response in people with posttraumatic stress disorder in conjunction with prolonged exposure therapy. Excitatory TI of the ventral striatum may be used in anhedonic depressed individuals to enhance effortful motivation during behavioral activation therapy. Given its depth and focality, non-invasive nature, minimal adverse effects, and use of relatively inexpensive equipment, TI may open new vistas for human cognitive neuroscience and neuromodulation interventions.

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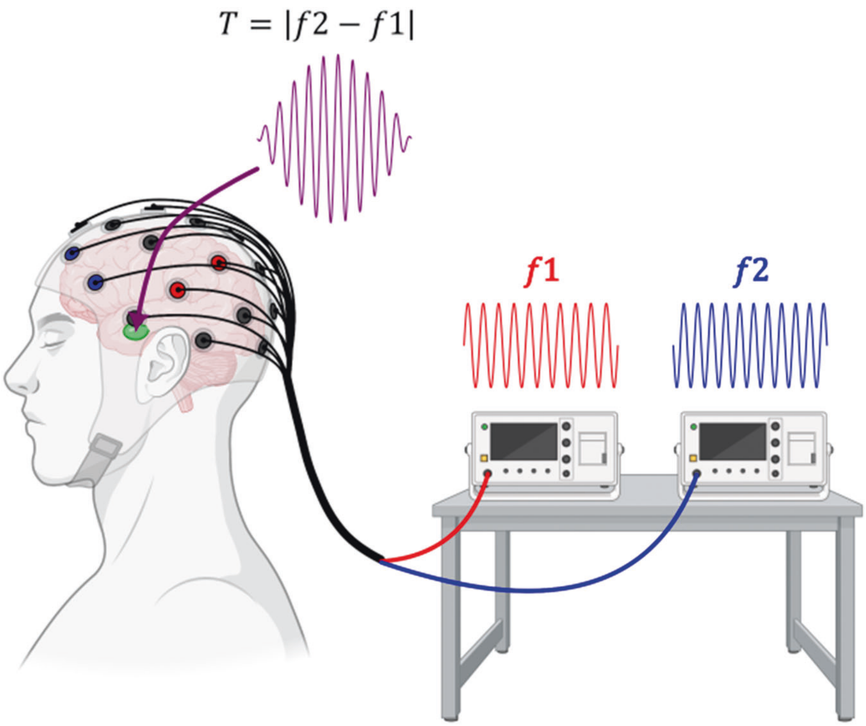

Fig. 1 Example of setup for inhibitory temporal interference with the amygdala. Two electric fields (*f*1, *f*2) deliver inhibitory stimulation to the amygdala at extra-physiological frequencies, (e.g., *f*1 = 5000 Hz and *f*2 = 5160 Hz), where T is the target frequency that represents the difference between the two (e.g., 160 Hz).

REFERENCES

1. Grossman N, Bono D, Dedic N, Kodandaramaiah SB, Rudenko A, Suk HJ, et al. Noninvasive deep brain stimulation via temporally interfering electric fields. Cell. 2017;169:1029–41.e16.
2. Hutcheon B, Yarom Y. Resonance, oscillation and the intrinsic frequency preferences of neurons. Trends Neurosci. 2000;23:216–22.
3. Mirzakhalili E, Barra B, Capogrosso M, Lempka SF. Biophysics of temporal interference stimulation. Cell Syst. 2020;11:557.
4. Acerbo E, Jegou A, Luff C, Dzialecka P, Botzanowski B, Missey F, et al. Focal non-invasive deep-brain stimulation with temporal interference for the suppression of epileptic biomarkers. Front Neurosci. 2022;16:945221.
5. Ma R, Xia X, Zhang W, Lu Z, Wu Q, Cui J, et al. High gamma and beta temporal interference stimulation in the human motor cortex improves motor functions. Front Neurosci. 2021;15:800436.
6. Piao Y, Ma R, Weng Y, Fan C, Xia X, Zhang W, et al. Safety evaluation of employing temporal interference transcranial alternating current stimulation in human studies. Brain Sci. 2022;12:1194.

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

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ADDITIONAL INFORMATION

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