VIEWPOINT

Translating Temporal Interference Brain Stimulation to Treat Neurological and Psychiatric Conditions

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Deep brain stimulation (DBS) has helped more than 100 000 patients with conditions such as Parkinson disease, essential tremor, dystonia, and obsessive-compulsive disorder, and it holds great potential for other conditions, such as depression and other neuropsychiatric disorders. The delivery of DBS requires an invasive implant, and this presents the potential for surgical complications.[1] Changing the stimulation target is also limited given the local nature of the implant. Noninvasive brain stimulation methods, such as transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES), have been used in many clinical and neuroscientific investigations and do not require surgery.[2] Noninvasive methods easily permit changes in the stimulation target. However, for TMS or TES to directly stimulate deep brain structures requires stronger stimulation of overlying (eg, cortical) areas, which may result in unanticipated adverse effects and encroach on safety guidelines.[3] Ideally, technology would offer the focality of DBS but the noninvasiveness of TMS or TES. Developing such a device would require invention, experiments, and clinical trials. These could be facilitated by collaboration between inventors and clinicians and partnerships with funders (eg, the National Institutes of Health).

Using mice as a model system, we have shown[4] it is possible to sculpt the time dynamics and geometry of applied electric fields to enable more focal noninvasive electrical neural stimulation. By delivering multiple electric fields to the brain at slightly different high, kilohertz frequencies, which are individually too high to recruit effective neural firing but in which the difference frequency is low enough to drive neural activity, neurons can be electrically activated at the locus where multiple electric fields overlap without strongly recruiting neighboring or overlying regions. This method is called temporal interference (TI) stimulation because focal stimulations are obtained at the site where multiple electric fields interfere; neural stimulation occurs where the amplitude of the electric field envelope at the difference frequency is of great magnitude.[4]

Interferometrically generated low frequencies have been shown to effectively drive neural activity in anesthetized living mice stimulated via electrodes applied to the skull, with responses recorded via automated in vivo whole-cell patch clamping.[4] Neurons followed the low-frequency envelope of the interfering electric fields but not the high-frequency carrier. For example, applying 2-kHz and 2.01-kHz currents recruited neurons to fire at the difference frequency (10 hertz), but applying 2-khz currents alone was ineffective.

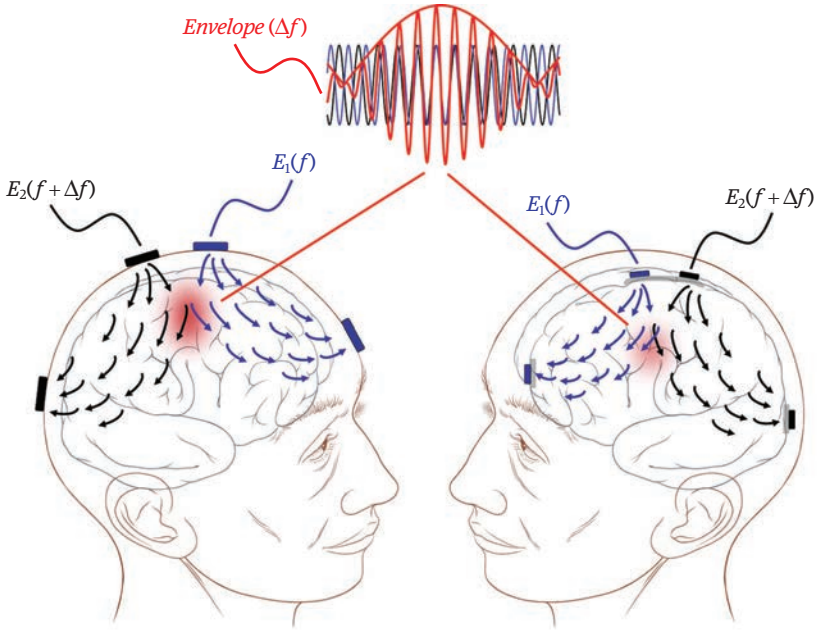
To test whether TI stimulation could recruit deep brain structures without overlying regions, we targeted TI stimulation via skull electrodes to the hippocampus of anesthetized living mice. The resultant activation profile was measured using c-Fos staining. Transcranial stimulation at 10 Hz resulted in broad c-Fos expression in the cortex and hippocampus. In contrast, TI stimulation (2 kHz + 2.01 kHz), with electrodes placed so that the envelope amplitude peak would be deeper than the cortex, resulted in c-Fos expression in the hippocampus with little or no expression in the overlying cortex. Immunohistochemical examination of various cellular and synaptic markers of cell damage, cell death, or inflammation revealed intact neuronal and synaptic integrity 24 hours after stimulation.

To test whether TI stimulation could functionally map a brain region without physically moving the electrodes, we stimulated the forelimb region of the motor cortex in anesthetized mice and measured their movements. Applying TI stimulation resulted in movements of the forelimb contralateral to the targeted motor cortex at the difference frequency. When the current above the forelimb area of the motor cortex was systematically increased and the current above the whisker area of the contralateral motor cortex was decreased with the sum fixed, the movement shifted to the paw and whisker contralateral to the second area.

The intrinsic low-pass filtering property of the neural membrane, which renders high-frequency depolarizations ineffective,[5] might explain the relative lack of electrophysiological effect by kilohertz-frequency electric fields in the absence of interference. A nonlinear response to the electric fields[6] could give rise to an electric field component that oscillates at the difference frequency, which would not be attenuated by the intrinsic low-pass filtering of the neural membrane.

In contrast to traditional electrical stimulation, the location of the stimulation effect (ie, the locus of peak envelope modulation) depends on the relative amplitude and orientation of the multiple applied currents. Thus, by varying the relative locations and currents of the electrode pairs, essentially any point in a 3-dimensional volume could be the locus of peak envelope modulation, albeit with a tradeoff between locus depth and breadth and strength. For example, steering the peak envelope modulation to the center of a cylindrical tissue phantom resulted in an envelope locus (ie, a distance out to 1/e of the envelope maximum) that was about 2 times larger than and had peak envelope amplitude 10 times weaker than the envelope locus obtained when the peak envelope modulation was steered to a location near the phantom surface (**Figure**). It might be possible to pinpoint smaller regions deep in the brain by using a larger number of interfering kilohertz-frequency electric fields, contingent on neurons making similar responses to the individual fields of different frequencies.[7]

Figure. Temporal Interference Brain Stimulation



Electric field vectors E_1 (blue arrows) and E_2 (black arrows) simultaneously applied to the brain via scalp electrodes (left panel) or via subdural electrodes (right panel) at kilohertz frequencies f_1 and f_2 that are higher than the range of frequencies of normal neural operation, but with a difference frequency (Δf) within that range. The superposition field (red trace) drives neural activity at the difference frequency Δf only in a small locus where the envelope amplitude is sufficiently large.

Temporal interference stimulation cannot currently match the spatial resolution of implantable DBS at depth. Preliminary finite element modeling simulations of TI fields in human anatomical models show that the locus of TI stimulation is comparable in size with large subcortical structures (eg, the hippocampus) or with deep structures with a preferential current pathway (eg, the anterior cingulate cortex) but cannot be localized to very small deep brain structures (eg, the subthalamic nucleus). Also, TI stimulation will require large-current amplitudes to achieve noninvasive suprathreshold stimulation of deep brain structures. That the locus of TI stimulation occurs remotely from the scalp may enable the use of stronger currents without compromising safety or inducing discomfort from extraneous activation of cutaneous neurons; however, validation of such a procedure requires rigorous testing. In the future, it might be possible to create minimally invasive TI stimulation interfaces in which the focus and strength of TI stimulation at depth is optimized with a subdural electrode configuration that bypasses losses in the scalp and skull. Such a minimally invasive setup might support clinical applications (eg, DBS for Parkinson disease) requiring continuous stimulation infeasible with noninvasive devices too bulky or cumbersome for continuous wear.

In summary, TI stimulation may in principle be capable of focal deep stimulation. Further work refining the invention is required to optimize it for human use. Trials are needed to understand TI stimulation outcomes in specific disease states. Regions that are deep but not too small as a fraction of total tissue volume (eg, those in stroke, obsessive-compulsive disorder, epilepsy, depression, and spinal cord injury) may be attractive initial indications.

ARTICLE INFORMATION

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Correction: This article was corrected on November 12, 2018, to change the corresponding author from Dr Okun to co– corresponding authors Drs Grossman and Boyden and to add the words "Imperial College London" after "United Kingdom Dementia Research Institute" in the author affiliations section.

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