Modulation without surgical intervention

Noninvasive deep brain stimulation can be achieved via temporally interfering electric fields

By Nir Grossman

A multitude of brain disorders have debilitating impacts on the quality of life of a large patient populace, accounting for ~30% of the global burden of disease (1). Most patients with brain disorders are unamenable to any form of treatment when first- and second-line interventions are ineffective (2, 3). Neuromodulation technologies can help millions of patients who suffer from such brain disorders.

Deep brain stimulation (DBS) has proven highly effective in treating Parkinson's disease and obsessive-compulsive disorder (4) and shows great potential for other conditions, such as depression (5). However, being a surgical procedure, the deployment of DBS is limited by the potential for complications (6).

Transient noninvasive brain stimulation methods, such as transcranial magnetic stimulation (TMS) (7) and transcranial electrical stimulation (TES) (8), have been used in many human clinical and neuroscientific investigations. However, the ability of TMS or TES to directly stimulate deeper brain structures is achieved at the expense of inducing stronger stimulation of the overlying cortical areas, resulting in wider stimulation of these areas, which may approach the limits of safety guidelines (9). Recently proposed methods for noninvasive DBS, for example, using transcranial ultrasound (10) or the expression of heat-sensitive receptors and injection of thermomagnetic nanoparticles (11), may have limited immediate use in humans owing to the poorly understood mechanism of action (12) and the need to genetically manipulate the brain, respectively.

TEMPORAL INTERFERENCE: A NEW METHOD OF BRAIN STIMULATION

We recently discovered a strategy for sculpting electrical fields to enable focused yet noninvasive neural stimulation at depth (13). By delivering multiple electric fields to the brain at slightly different frequencies within the kHz range—which are themselves too high to recruit effective neural firing, but for which the difference frequency is sufficiently low to drive neural activity—neurons can be electrically activated at a selected focus without driving neighboring or overlying regions. We call this method temporal interference (TI) stimulation, because the interference of multiple electric fields is what enables the focality.

We validated that interferometrically generated low frequencies could effectively drive neural activity by applying transcranial TI stimulation to anesthetized mice and recording the responses using a whole-cell patch-clamp technique. We found that neurons followed the low-frequency envelope of the electric fields but not the high-frequency carrier. For example, neurons experiencing 2 kHz and 2.01 kHz would fire at the difference frequency, 10 Hz, but were unresponsive to the 2-kHz carrier frequency.

TI CAN TARGET SUBCORTICAL STRUCTURES WITHOUT STIMULATING THE OVERLYING CORTEX

To test whether this method can be used to recruit deep brain structures without recruiting the overlying neural layers, we applied transcranial TI stimulation and control stimulation conditions to the hippocampus of anesthetized mice and subsequently measured the brain activation profile by staining for the immediate-early gene c-fos. We found that 10-Hz transcranial stimulation resulted in very broad c-fos expression profiles, with strong activation in the cortex and hippocampus. By contrast, transcranial application of 2 kHz + 2.01 kHz TI stimulation, with an envelope amplitude peak deeper than the cortex, resulted in c-fos expression only in the hippocampus with no appreciable neural activation in the cortex.

MOTOR CORTEX ACTIVATION CAN BE ADJUSTED WITHOUT MOVING ELECTRODES

To determine whether TI stimulation can evoke a behavioral response, we stimulated the forelimb region of the motor cortex of the anesthetized mice and measured the evoked motor activity. We found that simultaneous application of two currents, i.e., I1 and I2, at the same frequency of 2 kHz did not evoke motor activity. However, when the frequency of current I1 was set to 2.001, 2.005, or 2.01 kHz while keeping the frequency of current I2 fixed at 2 kHz, the stimulation evoked movement in the contralateral forelimb at the difference fre-
To test whether the evoked movement could be adjusted without physically moving the electrodes, we systematically increased the current $I_1$ above the forelimb area of the motor cortex and decreased the current $I_2$ above the whisker area of the contralateral motor cortex, keeping the current sum $(I_1+I_2)$ fixed. We found that the movement amplitude of the contralateral paw decreased and that of the contralateral whisker increased. When $I_1$ was larger than $I_2$, the stimulation evoked a movement in the whisker ipsilateral to $I_1$ electrodes, with stronger movements evoked as the amplitude of $I_1$ increased compared with $I_2$. This suggests that the steering effect anticipated in our model (13) could indeed be realized in vivo.

### SEARCHING FOR A MECHANISM

The intrinsic low-pass filtering of the neural membrane, which renders high-frequency depolarization ineffective (14), explains the lack of electrophysiological effect by kHz-frequency electric fields without TI. Future studies may investigate whether low-pass filtering changes at higher field magnitudes, addressing earlier reports that very strong kHz-frequency electric fields (one to two orders of magnitude stronger than those used in our study) can block the propagation of compound action potentials in peripheral nerves (15).

The intrinsic low-pass filtering of the neural membrane alone cannot explain the ability of temporally interfering kHz-frequency electric fields to drive neural activity, because it would equally attenuate the low-frequency changes in the envelope amplitude of the superimposed fields (16). In this case, a nonlinear response to the electric fields (17) can give rise to new field components, including an electric field component that oscillates at the difference frequency. Such a low-frequency electric field would not be attenuated by the intrinsic low-pass filtering of the neural membrane and might be rectified, for example, by ion-channel dynamics (18).

### FOCAL PRECISION AND TI STIMULATION

In contrast to traditional electrical stimulation, the stimulus location (i.e., the peak envelope modulation) of temporal interference depends on the relative amplitude and orientation of the applied currents. Thus, by varying the relative currents and locations of the electrode pairs, essentially any point within a three-dimensional volume could be targeted for peak envelope modulation.

models shows that the TI stimulation locus can be roughly localized in large subcortical structures (e.g., the hippocampus) or in subcortical structures with preferential current pathways (e.g., the anterior cingulate cortex), but cannot be localized in very small and deep brain structures, such as the subthalamic nucleus.

In addition, TI stimulation requires large current amplitudes to achieve supra-threshold stimulation of deep brain structures noninvasively. In the future, it might be possible to achieve tighter focus and stronger TI locus at depth with a subdural electrode configuration that bypasses the current shunting at the scalp–skull interface (19). A minimally invasive configuration might be advantageous in clinical applications, such as in Parkinson’s disease, that require continuous stimulation.

In summary, TI is a new brain stimulation modality whereby neural activity can be modulated by the application of multiple kHz-range electric fields. We have shown that TI stimulation can drive action potential activity in the live brain, recruit deep brain structures without the overlying cortical layer, and functionally map a brain region without physically moving the electrodes. We hope that the fact that TI stimulation uses well-known electrical fields and does not require chemical or genetic manipulation of the brain tissue will help speed up its clinical deployment, where it may benefit the large patient population in need of neural therapy.

### REFERENCES

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