

A Deeply Superficial Brain Stimulation

Grossman N, Bono D, Dedic N, et al. Noninvasive deep brain stimulation via temporally interfering electric fields. *Cell* 2017;169:1029-1041.

Deep brain stimulation (DBS) to modulate subcortical circuit activity is an efficient treatment for Parkinson's disease, essential tremor, and dystonia. DBS requires placing electrodes in the brain, with potentially severe complications.¹ There is therefore keen interest in developing noninvasive techniques.

In a recent issue of *Cell*, Grossmann et al presented a proof of principle for noninvasive yet spatially focused electrical stimulation to modulate neural circuits in mice. They cleverly exploit a simple principle of physics, whereby 2 electrodes attached to the surface of the head deliver transcranial alternating currents of very high but slightly different frequencies. This creates temporal interferences (TI) in the target area at a frequency that can entrain neuronal firing.

The authors first validated their approach in a computer model and by carrying out biophysical measurements in a dummy. They confirmed that the envelope of the interference had a frequency equal to the difference of the frequencies of the mother stimulations, which were chosen such that neurons could not follow (eg, 2000 versus 2010 Hz). Electrophysiological recordings in mice verified that neurons fired with the predicted frequency (ie, 10 Hz). Placing the extracranial electrodes at various locations on the surface of the skull could steer the focus of the interference to brain areas of interest. For example, aiming TI at the hippocampus, activity was recorded in the target but not in the overlying cortex.

Transcranial magnetic or electrical stimulation, the currently existing noninvasive techniques that modulate pathological circuit activity, can only target structures up to a couple of centimeters below the cortex.² In contrast, TI could allow for focused modulation of deep brain regions. Thanks to its reversibility, steerability, and noninvasive character, TI has the potential for novel indications, including obsessive-compulsive disorder, addiction, and depression, where patients are often hesitant to undergo surgery.

However, several questions remain. Can TI modulate deeper brain structures, such as the subthalamic nucleus,

which in humans lies several centimeters below the skull? Is it possible to mimic canonical DBS, which uses continuous stimulation at 80 to 165 Hz?³ Can spatial resolution be improved, perhaps by using multiple surface electrodes? What will the future TI-delivering device look like, and will it be suitable for clinical applications? Efforts to solve these questions need to be paralleled by research on the nature of the circuit dysfunction that ultimately is responsible for the symptoms. Cellular mechanisms underlying pathological neural networks will provide blueprints for novel DBS protocols.⁴ There is no doubt in our mind that publications such as the one by Grossmann et al will lead the way to expanding neuromodulation for novel indications based on mechanistic insight. ■

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