Trends in Cognitive Sciences

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Spotlight

Cross-Species Neuromodulation from High-Intensity Transcranial Electrical Stimulation

Alik S. Widge[1,2,*]

Transcranial electrical stimulation (TES) is a proposed tool for noninvasively modulating human brain circuits, but its ability to affect cortical physiology remains unclear. A recent study merged TES with live animal and human cadaveric recordings to verify intracranial electrical effects, then used these findings to develop a novel neuromodulation protocol.

Modern neuroscience increasingly focuses on circuits, with increasingly rapid progress in dissecting brain networks. It has been challenging to translate that progress into new therapies for brain disorders because human circuit manipulation tools are limited. Deep brain stimulation has shown some success [1], but this type of invasive therapy cannot address the vast clinical need. Brain disorders, particularly mental illnesses, strike millions of people per year. A better clinical circuit intervention would be noninvasive and could be self-administered by patients at home. Similarly, human neuroscience might be greatly advanced by a tool that could manipulate brain states without the seizure risk and expensive equipment associated with transcranial magnetic stimulation. Transcranial electrical stimulation (TES) might meet these needs. TES delivers electrical current through two or more scalp electrodes and is believed to alter cortical excitability in the regions directly beneath those electrodes. The relative safety and ease of use of TES have spurred great interest, with many small clinical trials in a variety of brain illnesses [2] and rapidly growing use in cognitive neuroscience experiments [3].

Those studies have equivocal and contradictory results [4,5]. This is in part because we do not know how TES actually affects the brain, or even whether TES current reaches its presumed target [2,6,7]. Subcranial cerebrospinal fluid (CSF) could shunt current back to the return electrode before it reaches the cortex. Recently, an international collaboration sought to measure both the electrical reach of TES and its effects on neurophysiology in both laboratory animals and humans. Vöröslakos *et al.* [8] applied TES to anesthetized rats and, recently, to postmortem (unfixed) human cadavers. In both preparations, they recorded intracranially at multiple locations to map the voltage gradient. They further compared stimulation at the skull surface (a common animal preparation) with true TES through the scalp (the standard human preparation). Their results confirm the cautions previously raised by modeling studies: much of the current applied through a scalp electrode never reached the target cortex. More than 80% of the applied current was lost in the rat. In human cadavers, the loss was closer to 60%, but the authors caution that even relatively fresh cadavers are dehydrated (therefore with less CSF to shunt through) compared with living humans.

Consistent with this, only the highest amplitudes of scalp-applied stimulation had any effect on recorded spiking in nearby cortex. To establish cross-species scaling, Vöröslakos *et al.* suggested the electric field voltage gradient as a reference point, on the grounds that this gradient may be a primary driver of voltage-sensitive membrane channels. From their rat preparation, they concluded that field gradients of 1–2 mV/mm are necessary to change firing rates. Even these may not be sufficient to drive large-scale ensemble activity; fields above 2 mV/mm did not affect oscillatory membrane potential fluctuations, even if they changed single-neuron spiking rates. On the basis of the cadaver studies, Vöröslakos *et al.* concluded that applied scalp currents of 6 mA or higher would be needed in humans to drive human cortical spiking, threefold higher than the standard 2 mA limit. Those higher currents are challenging to test in humans. Individual variability in shunting/spreading from scalp, skull, and CSF could move depolarization away from the intended target, diluting the experimental signal.

Vöröslakos *et al.* addressed this by proposing a more focal approach to TES, dubbed intersectional short pulse (ISP). ISP rapidly switches current between electrodes arrayed on two sides of a cortical target (Figure 1A). In a fashion analogous to radiation therapy, this creates 'beams' of electrical current that intersect near the desired cortical focus. In theory, integrative properties of the neuronal membrane would limit depolarization to cells in this intersectional focus. Indeed, in the authors' rat preparation, cells ipsilateral to an ISP focus had higher firing rates than those contralateral, although only a minority of neurons showed this differential modulation. Following a long tradition of medical self-experimentation, three of the authors then tested ISP on themselves, determining that it was uncomfortable (sensations of dizziness and phosphenes) but not unsafe. In a further test with 19 human volunteers, a 1-Hz ISP substantially increased the power of the dominant eyes-closed alpha oscillation (Figure 1B) and entrained the alpha amplitude to the ISP phase (Figure 1C). ISP complements other intersectional approaches such as temporal interference stimulation [9], which has deeper brain penetration but possibly a slower time course. Unlike other TES strategies, ISP seemed to lack prolonged

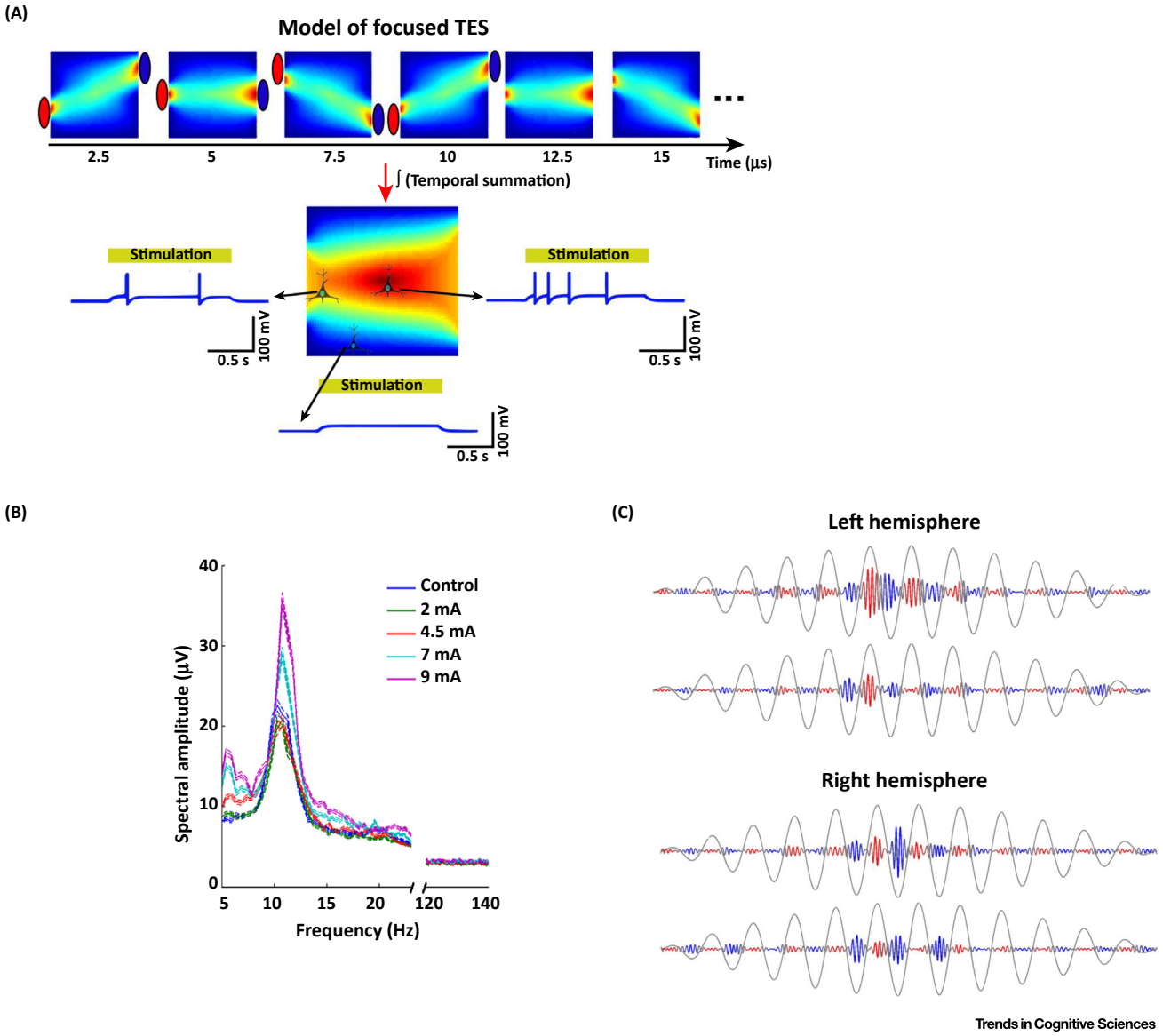

Figure 1. Modulation of Human Cortical Function by High-Intensity Intersectional Short Pulse (ISP) Stimulation. (A) Schematic of ISP approach. While a transcranial electrical stimulation (TES) waveform is being applied, the anode and cathode are switched every few microseconds between different opposing pairs of a multielectrode array. Colors indicate the expected electric field intensity in a plane connecting the two electrodes. In theory, the overlap of these 'beams' will create a focus of high effective field at the center of the array, with much lesser effect outside that focus. This is diagrammed in the bottom panel. (B) Dose dependence and specificity of ISP alpha-band modulation. In these example spectrograms from a single volunteer, increasing amplitudes of 1-Hz ISP TES enhanced the spectral alpha-band peak (at approximately 11 Hz). This increase was only seen for 7- and 9-mA ISP TES, consistent with the authors' claim that high current intensities are needed to depolarize cortex. High frequencies did not respond to TES. (C) Example of ISP phase entrainment of human alpha oscillations. Shown are two example eyes-closed recordings from P3 (left) and P4 (right) scalp electrodes in a single human volunteer. The black sinusoids represent the ISP TES waveform, a 1-Hz sinusoid that ramps from 0 to 7.5 mA peak current over 5 s. Blue and red colors on the EEG trace denote right-to-left and left-to-right current flow, respectively. The amplitude of the dominant alpha oscillation increases as the ISP TES amplitude increases, and this amplitude modulation phase-locks to the TES. Reproduced and adapted from [8] under a Creative Commons CC BY license.

poststimulation effects, possibly allowing focused manipulations during cognitive tasks. The main limitation of ISP is that it is readily detectable by almost all individuals, making blinding difficult.

The authors' results are both encouraging and disheartening. Encouraging, because they confirm that transcranial currents of sufficient magnitude can indeed alter physiology. Although the ISP protocol of Vöröslakos *et al.* was clearly palpable (raising the possibility of an expectancy/arousal effect), an increase in eyes-closed alpha is difficult to explain as mere arousal. The cross-species identification of an approximate threshold for TES-induced neural excitation should also improve translational studies. Disheartening, because they raise the possibility that much of the extant TES research involved stimulation of something other than cortex. On the other hand, even if 1 mV/mm is a threshold for neuronal depolarization, 0.25 mV/mm (the effective gradient from 2 mA TES in this study) might affect cells that are properly oriented relative to the applied field, or that are already depolarized. Other investigators report higher voltage gradients *in vivo* in humans from 1–2 mA TES [6,7]. Further, many studies show excitability changes long after 1–2 mA TES ends, which cannot be explained as filter artifact [3,4]. Further intracranial recordings should clarify the limits of TES. There is already great interest in realistic head models that predict the intracranial fields arising from a given scalp montage. Cadaver recordings could validate and refine such models, allowing investigators to better assess TES study designs for target engagement. *In vivo* human recordings, such as those routinely collected in epilepsy patients, are also being used for validation [7]. Collectively, these studies are rapidly moving us towards a more rational and well-informed use of TES as a scientific and clinical tool.

[1]Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
[2]Picower Institute for Learning & Memory, Massachusetts Institute of Technology, Cambridge, MA, USA

*Correspondence: awidge@partners.org (A.S. Widge).

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