PRIZE ESSAY

GRAND PRIZE WINNER

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www.science.org/doi/10.1126/science.add4834

FINALIST

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www.science.org/doi/10.1126/science.add4836

NEUROMODULATION

Synchronizing neural rhythms

Personalized, noninvasive network-based neuromodulation aids impaired cognition

By **Robert M. G. Reinhart**[1,2]

Cognitive brain disorders are among the most disabling health states in the world. Existing pharmacological, surgical, and behavioral therapeutic approaches for impaired cognition are limited by heterogeneous treatment outcomes, slow symptom resolution, and accompanying risks and side effects. Consequently, there is an urgent need to develop innovative and personalized therapeutic interventions that are capable of providing rapid and sustainable improvements with minimal side effects. Noninvasive neuromodulation technology is an emerging class of tools that offer such translational potential for neurocognitive disorders. Tools such as high-definition transcranial alternating current stimulation (HD-tACS) offer unprecedented control in modulating rhythmic activity in cortical regions that are implicated in neurocognitive dysfunction (*1*). Our latest research in precision or personalized HD-tACS shows promise at noninvasively manipulating neural population dynamics and improving human cognition and adaptive behavior in a selective and long-lasting fashion (*2*–*5*).

Our neuromodulation design is grounded in fundamental neuroscience research that views cognition as arising from synchronous electrophysiological rhythms across multiple spatiotemporal scales (*2*, *4*–*6*). Neural rhythms derive from inhibitory and excitatory postsynaptic currents and are evident as cyclic changes in the voltages of local field potentials, electrocorticograms, electroencephalograms, and magnetoencephalograms. Functionally, synchronized rhythms sculpt neurophysiological dynamics to facilitate precise yet flexible communication necessary for goal-directed action and cognition (*1*, *6*). This synchronization is achieved by gating information transmission during windows of high excitability through transient, phase-coordinated local neuronal spiking within and across neuronal networks. By coordinating spike timing, synchronization increases the likelihood of inducing spike timing–dependent plasticity, thereby promoting flexible cognitive function. As a result, neural synchronization is recognized as a fundamental neurophysiological process that is necessary for human cognition.

The synchrony of neural rhythms within or between cortical regions can be changed noninvasively using tACS. This technique delivers low-intensity alternating currents on the scalp using a predetermined topographical arrangement of electrodes to induce alternating electric field gradients in a target brain region. These alternating electric fields manipulate spike timing through phase alignment of neuronal activity, without necessarily affecting the spiking rate of the neuronal population (*7*). The entrainment of neuronal activity can lead to the induction of neuroplasticity, which allows any neural and cognitive changes to persist beyond the duration of neuromodulation. Moreover, simultaneous application of two (or more) tACS currents targeted to different brain regions can be used to modulate phase synchronization among them (*3*). Thus, tACS can be used to noninvasively manipulate synchronized rhythmic activity within and between cortical networks.

Advances in tACS technology and protocol design offer expanded functional and anatomical targeting over conventional tACS. Multichannel HD-tACS designs, which involve substantially smaller electrodes arranged in a center-surround configuration, have been shown to produce more focal stimulation in cortical targets (*8*). The spatial arrangement of these electrodes on the scalp is guided by computational models of electric fields, which further improves the focality of stimulation (*8*). Enhanced focality minimizes the likelihood of producing unwanted effects in other anatomical structures such as the retina or the extracranial tissue. Recently, considerable attention has been devoted to the personalization of HD-tACS (*9*). Here, key properties of individual neurophysiology such as anatomical variability or intrinsic rhythmic frequency of a neural circuit are considered. Using a combination of these developments, we have demonstrated effective, functionally specific, bidirectional, and long-lasting control over network synchronization patterns that support cognitive function (*2*–*5*, *10*, *11*). The integration of these advances into the development of personalized, highly fo-

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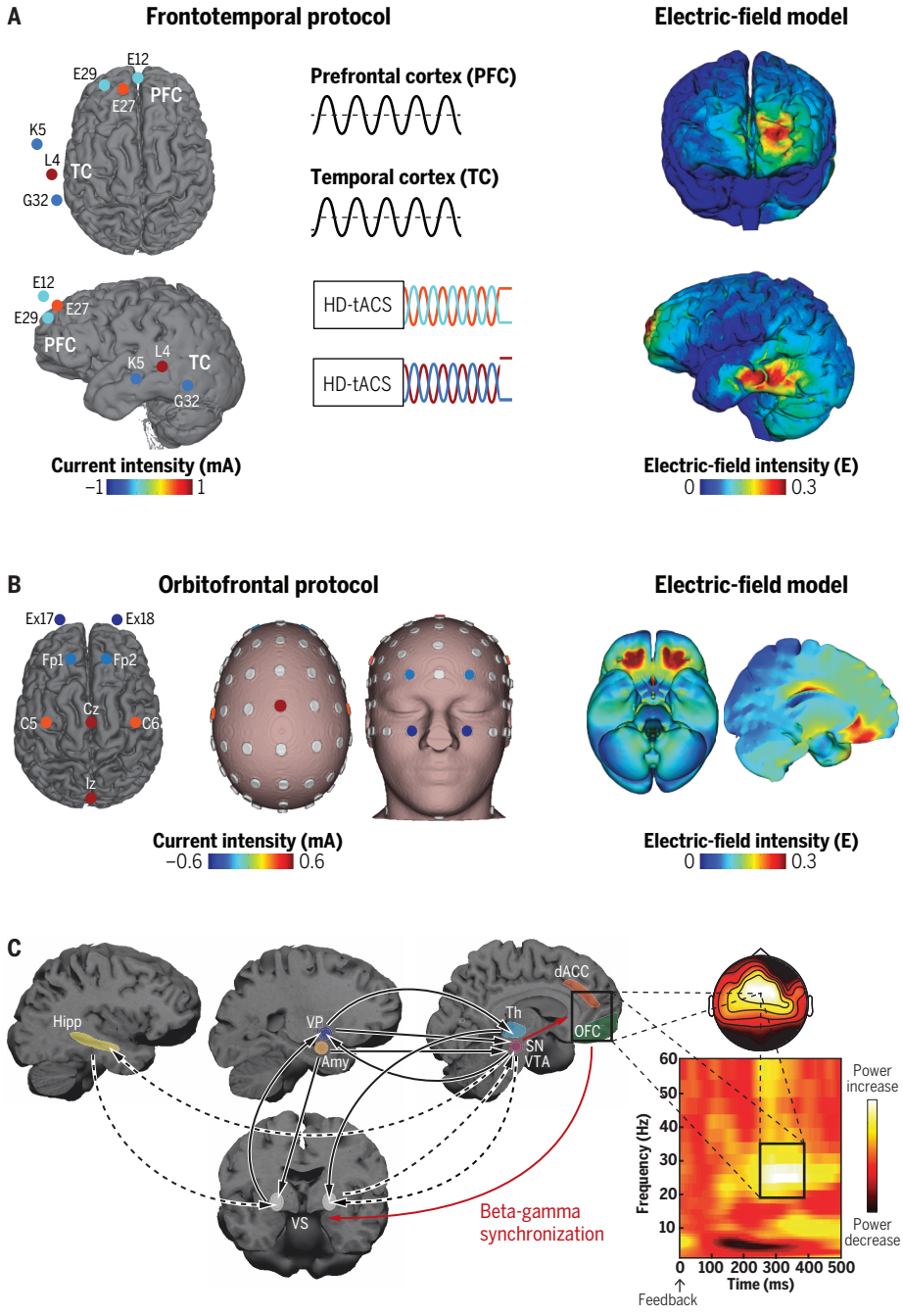

Multichannel high-definition frontotemporal (A) and orbitofrontal (B) neuromodulation protocols and electric-field models for high-definition transcranial alternating current stimulation (HD-tACS) are shown. The colored circles indicate electrodes. Network integrating reward and learning circuitry showing the reward feedback beta-gamma effect that is hypothesized to rise from the orbitofrontal cortex (OFC) and synchronize with the ventral striatum (VS) via beta-gamma rhythms is presented in (C). Amy, amygdala; dACC, dorsal anterior cingulate cortex; Hipp, hippocampus; SN, substantia nigra; Th, thalamus; VP, ventral pallidum; VTA, ventral tegmental area.

cal designs offers a promising opportunity to better steer the plasticity mechanisms of human cognition.

We recently discovered that synchronization-dependent neural coding schemes underlie poorer memory function in people aged 60 to 76 years and developed advanced neuromodulation protocols that target these motifs for memory enhancement (see the online figure, top). Before neuromodulation, these individuals showed poorer working memory performance compared with younger adults (*2*). These impairments were found to be associated with reduced theta-gamma phase-amplitude coupling (PAC) in the temporal cortex (*2*). PAC is a well-studied neural coding motif that occurs when the amplitude of a high-frequency rhythm synchronizes with the phase of a low-frequency rhythm. This form of synchronization facilitates the integration of information across spatiotemporal scales within a nested cortical network (*6*, *12*). We found that local PAC deficits in the temporal cortex arose because of deficient prefrontal control marked by reduced theta-phase synchronization between the frontotemporal areas. Phase synchronization—when two or more rhythmic neuronal signals tend to cycle with consistent relative phase—is another leading neural coding motif for coordinating spatiotemporal neuronal activity (*1*, *6*, *12*). These synchronization schemes thus serve as potential targets for neuromodulation to improve memory function.

Guided by electric field modeling, we developed a personalized HD-tACS protocol to rescue theta-phase synchronization in the frontotemporal cortex. The frequency of synchronization was individually determined for each participant to maximize the likelihood of entrainment. Simultaneous in-phase entrainment of both frontal and temporal regions at personalized theta frequencies induced in this manner restored intrinsic frontotemporal theta-phase synchronization, recovered the deficient theta-gamma PAC in the temporal cortex (see the online figure, top), and improved working memory performance in older adults (*2*). Even though neuromodulation was performed for ~25 min, improvements in memory function were sustained for at least 50 min, suggesting that the protocol produced neuroplastic changes outlasting the modulation period (*2*). Moreover, an additional experiment in younger adults with antiphase synchronization of frontotemporal regions demonstrated that memory performance can even be down-regulated. This finding suggests that cognitive function can be bidirectionally manipulated using phase-dependent interregional synchronization. This property of precision neuromodulation may be useful in pathologies where overactive memory processes need to be regulated, such as in posttraumatic stress disorder.

Our precision neuromodulation approach identified that it was essential to perform HD-tACS using personalized theta frequencies. By contrast, control experiments with a fixed theta frequency for all participants did not produce any improvements in memory function in older adults. Thus, advances in noninvasive neuromodulation that leverage the spatial and spectral parameters of individual neurophysiology offer a promising opportunity to effectively synchronize large-scale brain rhythms and rapidly improve memory function in older people. Such developments are especially valuable considering the rapidly aging global popu-

GRAPHIC: C. SMITH/*SCIENCE* BASED ON REINHART *ET AL.* (*2*) AND GROVER *ET AL.* (*4*)

lation and its associated personal, social, health care, and economic costs.

Current theories in biological psychiatry on the nature of compulsivity, including obsessive-compulsive disorder (OCD), view symptoms as outcomes of dysregulated habits and atypical reward processing due to abnormalities in cortico-basal ganglia networks (*13*, *14*). In parallel, fundamental neuroscience research has identified a neural signature in the form of medial-frontal beta-gamma rhythms, presumed to arise from the orbitofrontal cortex (OFC) during reward processing (see the online figure, bottom) (*15*). Combining these insights, we proposed that beta-gamma rhythms may constitute the neural code underlying orbitofrontal-striatal interactions that give rise to abnormal reward processing and OCD symptoms. To test this theory, we devised a personalized model-guided HD-tACS protocol for targeting individual beta-gamma rhythms of the OFC (see the online figure, middle) and demonstrated rapid, reversible, frequency-specific modulation of reward-guided choice behavior and learning in healthy young adults (*4*). Next, by repeatedly modulating personalized OFC beta-gamma rhythms over 5 days, we effectively reduced obsessive-compulsive behaviors in a nonclinical population. The rapid reduction in obsessive-compulsive behaviors—including hoarding, ordering, and checking—lasted for at least 3 months (*4*), and the largest improvements were experienced in people with more severe symptoms. These findings bode well for extending this personalized neuroscience intervention to people with clinical OCD and other compulsivity disorders, such as behavioral addiction (e.g., gambling, internet), eating disorders, substance use or abuse, and Tourette syndrome. More broadly, because the OFC is increasingly recognized to play a central role in the pathophysiology of mood, anxiety, psychosis, and other major categories of psychiatric disorders (*14*), the noninvasive procedure we developed for selectively modulating OFC beta-gamma rhythms could lay the basis for future nonpharmacological therapeutics that are applicable to a wide range of psychiatric illnesses.

The fields of fundamental and clinical neuroscience have made extraordinary advances in understanding the dynamic structure of the neuronal network activity that underlies cognitive function and dysfunction. Leveraging these insights has allowed us to develop neuromodulation protocols, personalized to individual neurophysiology, that can selectively augment components of rhythmic cortical networks and improve cognitive function and adaptive behavior in a rapid and sustainable fashion. Although it is challenging to predict the future, we are optimistic that personalization rooted in the neuroscience of network dynamics will rise to the forefront of next-generation noninvasive neuromodulation and pave the way toward future use of precision electroceuticals in neurology and psychiatry. ■

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ACKNOWLEDGMENTS

The research described in this essay was funded by grants from the National Institutes of Health (R01-MH-114877 and R01-AG-063775) and a generous gift from an individual philanthropist.

10.1126/science.add4834

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Science, 377 (6606), • DOI: 10.1126/science.add4834