

Enhancing cognition using transcranial electrical stimulation

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Noninvasive brain stimulation is being widely investigated to understand and modulate human brain function, and offers novel therapeutic approaches to neurologic and psychiatric disorders. Here, we focus on the growing interest in the potential of noninvasive brain stimulation, particularly transcranial Electrical Stimulation (tES), to enhance cognitive abilities in healthy individuals through the modulation of neuronal membrane potentials, specific brain oscillations or the delivery of electrical ‘noise’ to the system. We also emphasize the potential of tailoring tES parameters to individual trait and state characteristics for a personalized-medicine approach. Finally, we address the increasing use of tES by lay people, the ethical issues this raises, and consequently call for appropriate regulation.

Addresses

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Summary

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enhance cognitive abilities in healthy individuals through the modulation of neuronal membrane potentials, specific brain oscillations or the delivery of electrical ‘noise’ to the system. We also emphasize the potential of tailoring tES parameters to individual trait and state characteristics for a personalized-medicine approach. Finally, we address the increasing use of tES by lay people, the ethical issues this raises, and consequently call for appropriate regulation.

The expanding field of neuroenhancement using noninvasive brain stimulation

Is it possible to enhance human cognition and, if so, how? The answer to this question remains unclear, and yet, cognitive enhancement is a rapidly growing field of modern neuroscience, used both for rehabilitative and therapeutic purposes, as well as in attempts to enhance the cognition of healthy young adults. Potential interventions include tailored programs, adopted from the clinical field, for example, cognitive training, dietary regime, physical training, pharmacological agents, and, most recently, non-invasive brain stimulation (NIBS).

The efficacy of some interventions aimed at improving human cognitive functions has been disputed [1,2]. However, recent evidence demonstrates small, but significant effects for cognitive training (mainly working memory) [3]. Physical activity has also been shown to improve cognitive functions in healthy adolescents and the elderly, and to prevent cognitive decline in the latter [4–6]. Pharmacological agents are being investigated with regards to their potential to enhance cognitive functions [7,8]. Finally, attempts to use NIBS — specifically transcranial electrical stimulation (tES) — to potentiate human cognition date back to the Victorian time [9], but the last ten years have seen an exponential growth of technical progress, turning tES into a promising tools for modulation of neural activity, and thereby possibly enhancing cognitive abilities.

The mechanisms of cognitive enhancement using different approaches likely differ. Partly overlapping and not mutually exclusive neural mechanisms could account for enhancement of cognitive performance using different approaches, and their combination may thus be most effective. One might envision more efficient activation of neural structures recruited by a cognitive task resulting

in improved performance on that task. Alternatively, one can postulate that a net increase in more global brain resources would contribute to more wide-spread enhanced abilities. Importantly, facilitation on one cognitive task could happen with or without concomitant costs to other cognitive abilities and functions. Behavioral training probably depends on strengthening neural networks through repeated co-activations, while exercise and pharmacological interventions may work by manipulating available levels of neurotransmitters. tES techniques enable increasing or decreasing activity in specific brain regions and neural networks, induction of paradoxical facilitation by leveraging brain network dynamics, injection of small amounts of noise to maximize signal to noise ratio via stochastic resonance, entrainment of specific oscillatory patterns, and modulation of connectivity and plasticity across brain networks.

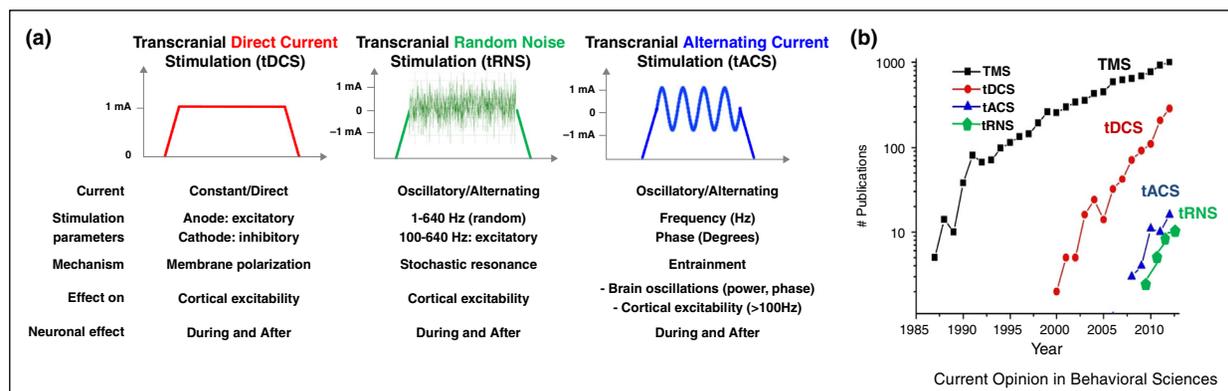
The most investigated of tES techniques, transcranial direct current stimulation (tDCS), was re-introduced in the 1990s after having been largely abandoned in the late 1960s [9]. Although its rather non-specific activation of underlying brain areas limits its potential as a diagnostic tool, tDCS has recently been investigated for the treatment of motor, perceptual, mood, and cognitive dysfunctions in patients. Initially, tDCS research with healthy participants was mostly designed as precursor for patient studies. However, following a series of promising results, interest in tDCS to potentially enhance brain function in healthy individuals has been rapidly growing. Technical

developments have led to the design and implementation of transcranial alternating stimulation (tACS) and transcranial random noise stimulation (tRNS) (see Figure 1 for a brief explanation of tES techniques), which are thought to engage different neural mechanisms than tDCS and also offer promise to enhance human abilities. It is also possible to combine tDCS with tACS (oscillatory tDCS, or osc-tDCS) adding a DC offset to the sinusoidal AC, therefore possibly exploiting the DC effect on cortical excitability and the AC synchronizing effect on rhythmic neuronal activity. This review will cover recent advances in neuroenhancement in healthy populations using tES, including a brief introduction to currently available techniques, an analysis of the most recent literature and summary of effects on various cognitive domains, a discussion of ethical issues, and finally an overview of potential future directions.

When cognitive training is not enough: new opportunities using tES

Given the assumption that brain training relies on the repeated activation of a specific neurocognitive circuit, which is sustained by well-orchestrated local and inter-regional activations, the idea of boosting such dynamics by acting on their neurophysiological substrate has materialized in the form of a pertinent body of research. Underlying neurophysiological mechanisms of learning and tES are thought to overlap, and their combination is therefore thought to lead to synergistic effects. Neurophysiological mechanisms underlying tES methods are

Figure 1



tES techniques. Current approaches include (a) direct current stimulation (tDCS), alternating current stimulation (tACS), and random noise stimulation (tRNS). Although tDCS is thought to influence neuronal firing rates by polarizing membrane potentials in a bimodal manner, tACS has been shown to up-regulate and down-regulate the firing rate without changing its average value, thus affecting neuronal spike timing [48]. tACS generates an alternating current at a specific frequency, with the potential to synchronize or desynchronize activity between targeted brain regions through phase-locking and coherence mechanisms. Given recent theories about neural populations communicating through time-locked oscillations [49], such capability of tACS can be exploited for tailoring individualized interventions aimed at coupling or decoupling activity between specific brain regions. By contrast, tRNS involves the application of alternating currents at random frequencies. Due to its oscillatory, rather than direct current, nature, it has been proposed that tRNS is polarity-independent (i.e. neither anodal nor cathodal; [50]). High-frequency tRNS (from 100 Hz to 640 Hz) has been shown to elicit powerful cortical excitability modulations with respect to anodal tDCS, and even longer after-effects [51]. (b) The exponential growth of tES. Literature search was run on Medline database; search parameters were 'repetitive Transcranial Magnetic Stimulation', 'transcranial Direct Current Stimulation', 'transcranial Alternate Current Stimulation', 'transcranial Random Noise Stimulation' and their acronyms (rTMS, tDCS, tACS, tRNS).

being investigated, with evidence to date suggesting that the effects are due to changes in neural activity in targeted brain areas and networks [10,11]. The mechanism of action of tDCS is thought to be mediated by ‘membrane polarization’, that is, an externally induced polarization of neuronal tissue with a consequent change in neuronal firing rates/threshold [12,13]. tACS [14] and tRNS [15] are thought to alter the brain’s intrinsic oscillations through frequency-specific entrainment, plasticity, or stochastic resonance resulting in an increase or decrease of the amplitude, coherence or phase of targeted brain rhythms [16]. Osc-tDCS is presumed to simultaneously manipulate both the cortical excitability and the spontaneous brain rhythms. Preliminary studies show positive results of tES in sensorimotor [17], visual [18] and cognitive [19*,20**,21*,22*] domains, and suggest that these newer methodologies may provide a flexible approach to directly investigate the effects of neural oscillations on behavior.

Combinations of tES with other interventions, for example, cognitive training, physical activity, or pharmacologic agents, offer the potential to maximize cognitive enhancement. This supports tES as one of the most promising approaches within the cognitive enhancement field: different from other interventions, which indirectly target specific brain activity patterns, for example, by promoting an unspecific increase in cerebral blood flow and nutrients (e.g. diet and physical training) or neurotransmitters (e.g. drugs, which also carry undesired side effects), tES allows for a more specific stimulation of brain regions responsible for the cognitive process at hand. Finely tuned tES montages and protocols will likely allow the reproduction of patterns of co-activation within a functional network similar as during cognitive training. Furthermore, repeated strengthening of interregional coupling at rest is hypothesized to be a potential primer to increase efficacy of other cognitive enhancement approaches. Finally, even though a healthy dietary regime and physical activity are strong promoters of well-being and should be encouraged, their effects come with an higher level of commitment in terms of dedication and time. tES could allow to achieve similar cognitive effects with portable, easy to use devices which could be used by individuals unable to follow a specific program due to physical or psychological impairments (e.g. elderly or patients with disabilities). Along with practical features (e.g. ease of use, portability, safety) and considering its early stage of development, tES might represent the best tool for non-invasive cognitive enhancement in humans both alone and combined with other interventions. Despite this promising scenario, it is still unproved ability to reliably target subcortical regions through both direct targeting (i.e. through specific montages resulting in current reaching its global maxima on specific structures below the cortical mantle) or indirect targeting (by leveraging on cortico-subcortical connectivity patterns), and the lack of robust knowledge about the

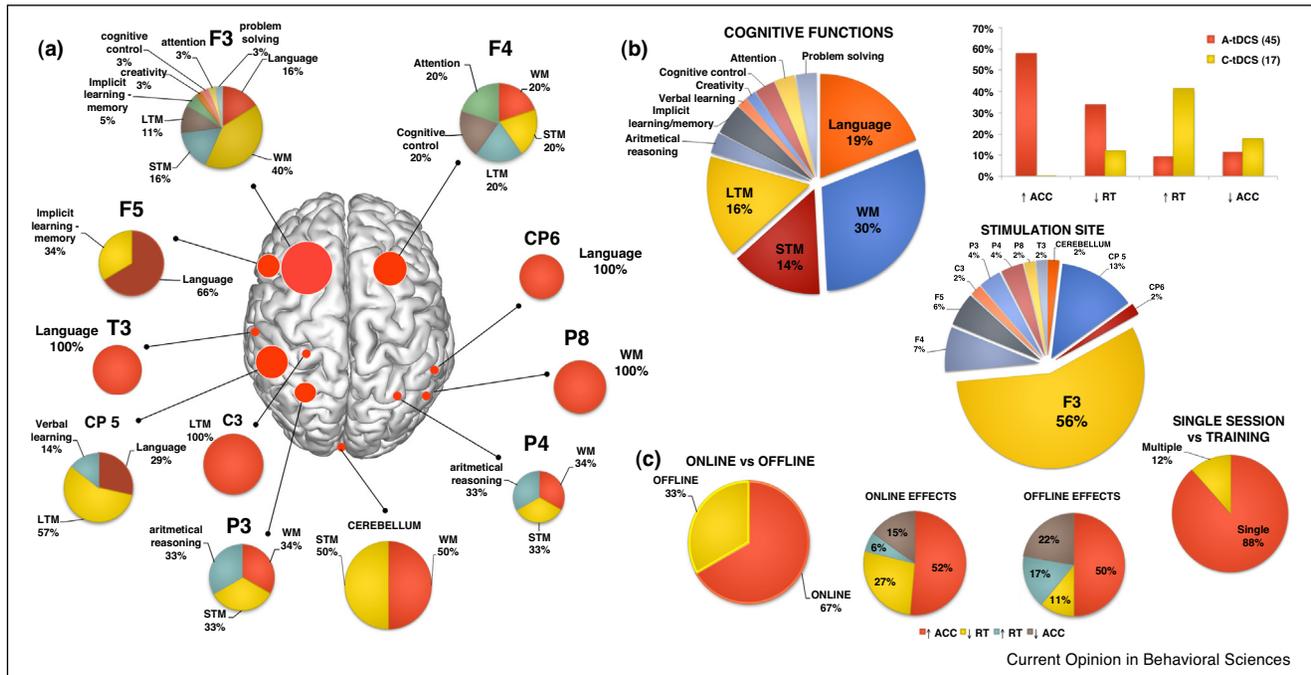
mechanism of action and neurobiological effects, emphasize the need for caution in interpreting the current available literature as well as advocating for their widespread use. Many questions remain underexplored, including how these effects may arise, whether they might be limited or modified by one’s cognitive capacities or reserves, system-inherent limitations and other state-related and trait-related factors.

Recent evidence of tES enhancement effects on cognition

Most published studies investigating tES effects on cognitive functions have used tDCS, but tACS, osc-tDCS and tRNS are gaining popularity (Figure 1b). tDCS has been applied in many cognitive domains (including substantial work in working memory, short-term and long-term memory as well as speech and language), with the polarity of stimulation and corresponding effects — i.e. cognitive enhancement is thought to be achieved by placing the anode or cathode over the cortical region (or network node) to be respectively increased or decreased in activity [23,24] (see Figure 2b) — being considered a fixed feature of such kind of intervention, making its application and the definition of experimental protocols a relatively straightforward task. However, recent evidence suggests new scenarios where the interaction between polarity, localization and timing of stimulation might induce unexpected, even counterintuitive results. Interestingly, several studies have reported paradoxical effects, with behavioral improvements induced by cathodal stimulation [25,26], as well as polarity non-specific effects where both anodal and cathodal stimulation seem responsible for a worsening of performance [25,27,28], emphasizing the need for revising current theories and models of tDCS mechanisms of action. It is important to remember that tDCS should not be conceived as a unitary intervention, but rather as a tool capable of altering activity in different brain structures, by increasing or decreasing their excitability, as well as by modifying the signal to noise ratio in the stimulated region. The specific effect is heavily dependent on variables such as stimulation montage and intensity, but also on intrinsic brain features like structural connectivity and the participation of the target region(s) in specific functional network(s).

A recent quantitative meta-analysis reported a lack of significant effect of tDCS on cognitive functioning when single session interventions are examined [29]. The null result in this study can be due to poor congruence between studies, small sample sizes in each cognitive domain (mainly 2–4 studies), and different study populations. Most importantly though, tDCS cannot be treated as a unitary intervention. One should avoid thinking of ‘anodal’ or ‘cathodal’ tDCS and instead emphasize the fact that tDCS exposes the brain to a field of current with specific directionality and differential impact on distinct

Figure 2



tDCS and cognition: a snapshot of the available literature. (a) The proportion of studies addressing different cognitive functions and targeting different brain regions of interest (the size of the circles on the brain surface represent the % of studies involving stimulation of the highlighted region). (b) The most investigated functions and stimulation sites, as well as the percentage of studies reporting changes in accuracy and/or reaction times for anodal and cathodal tDCS. Bars refer to the percentage of studies reporting an increase/decrease in accuracy/reaction time respect to the total amount of studies applying anodal or cathodal tDCS (in brackets), regardless of the cognitive function(s) being investigated). (c) An overview of the number of studies testing an online or offline tDCS effect, the corresponding average effect on accuracy and reaction being reported and the proportion of single and multiple session studies. Note: electrodes locations refer to the 10/20 international EEG system. WM: working memory; STM: short-term memory; LTM: long-term memory; ACC: accuracy; RT: reaction time; a-tDCS: anodal tDCS; c-tDCS: cathodal tDCS.

brain structures depending on stimulation parameters and electrode montage. Furthermore, the impact on the distinct brain structures is modulated by their state of activity, and precision in identifying differences between tDCS protocols is crucial to relate targeted brain structures with observed behavioral and cognitive effects. This seems to be a more realistic and sound approach that could help explain variability in study outcomes.

A crucial appeal of the potential of tACS is that it can be programmed to take into account the very precise rhythms that are crucial for normal brain function. Traditional pharmacological and other treatments, as well as tDCS and other forms of NIBS, are unable at present to address these very precise rhythms, which might be problematic because these rhythms seem to be crucial for normal cognition. However, we lack a mechanistic understanding of how the multiple, interlocking brain rhythms carry out cognitive processing in healthy individuals, and how these processes are impaired in individuals with mental illness. Furthermore, we need more insights into how to best target the stimulation so that

it takes advantage of intrinsic connectivity within the brain. Thus, a number of important steps are required to assess the true potential effectiveness of tACS, including the development of computational models of brain activity, as well as brain stimulation algorithms and hardware tools that can precisely modulate these rhythms and so change cognition. Nevertheless, tACS is being applied to enhance working memory and fluid intelligence, as well as attention and motor-imagery [20**,21*,30*,31], while tRNS has shown promising improvement effects in working memory, numerical abilities, and different learning paradigms [19,22*,32]. In order to explore behavioral effects whilst promoting more in-depth knowledge of the neurophysiological underpinnings an increasing number of studies combine electrophysiological recording with the stimulation to inform the tES protocols [20**,31]. Such experimental designs are likely to become crucial for future investigations moving toward individualized interventions.

Due to the still sparse knowledge about underlying neurophysiological effects of tES, it is also necessary to

foster the discussion raised in the last years about *state* and *trait* dependency of tES effects, a factor that likely contributes to the observed inhomogeneity in study outcomes. Various studies have highlighted the importance of monitoring individual factors such as gender, age, education, health status, brain physiology, and genetic polymorphisms, as well as keeping track of other possible ‘modulators’ like satiation level, amount and quality of sleep, energy level, mood, and metabolism-related factors [33]. Several studies have demonstrated that the effects of a single-session of tES can vanish in response to behavioral or cognitive priming [34,35], or lead to enhancement or impairment at the behavioral and physiological level due to individual trait [36]. Therefore, current evidence about tES in cognition should be carefully evaluated and when possible future studies should take individual state and trait into consideration.

Our discussion so far has been mainly limited to studies applying a single tES session, but the number of studies applying tES in combination with cognitive and motor training and in multiple sessions on consecutive or distributed days is increasing (Figure 2). Combining neuroplasticity-based effects of training with the additive value of electrical stimulation has proven to lead to larger effects than training alone [19,22*,37], also highlighting different interactions between training and stimulation protocols. Given the different mechanisms behind stimulation approaches, these kinds of studies could also indirectly help provide new knowledge about the neurophysiological underpinnings of learning processes themselves, adding even more value to the implementation of tES to study human cognition. However, the impact of repeated tES sessions on the brain is still not entirely clear, with unpredictable plasticity-based effects possible after weeks or months of stimulation. Future studies should deepen our understanding on such long-term effects as these are also important considering safety aspects, and to enable comparison of the effects of tES with those of other cognitive enhancement approaches.

Ethical and social issues

Noninvasive brain stimulation methods, particularly tES, are receiving increasing attention from the media, particularly given the findings on cognitive enhancement in healthy adults. Instructions on how to build your own tES device can be readily found on the internet and a number of companies offer inexpensive consumer devices for various applications such as to improve thinking speed, attention, and gaming performance [38]. In the wake of these developments, concerns are raised that modulating brain functions, especially over sustained periods of time, could have unforeseen and undesirable consequences [39]. A thoughtful and balanced ethical debate is crucially needed, and ought to include ethicists, scientists, clinicians, regulatory agencies, industry, patient advocacy groups, and representatives of the public in general.

The technology available on the consumer market and its possible use in healthy and vulnerable subjects, such as patients or children, does not appear to be sufficiently or appropriately regulated. Careful assessment of pertinent regulations differentiating between medical and enhancement uses seems needed [40–42].

Considerations of costs and benefits have to inform the ethical dialog. Cognitive enhancement as such is only valuable if costs are taken into consideration [43*]. Cost–benefit interactions may occur at different systemic levels, ranging from neuronal processes to network interactions and behavioral outcomes, lastly reaching the societal level [44]. Furthermore, the timing of benefits and costs may vary, with potentially short-term benefits being offset by longer-term risks. More studies are needed to fully assess the lifespan risk–benefit balance of tES approaches for neuroenhancement across target populations. The question of cognitive inequality can be related to biological or societal differences. At a biological level, individual traits could determine who profits from cognitive enhancement. At a societal level, inequality could originate from limited access to cutting-edge stimulation technology or patented protocols, despite the recent diffusion of do-it-yourself solutions for homemade stimulation.

Future directions

Recent advances in the field of connectomics and mathematical modeling of current flow are opening new opportunities to tailor tES interventions on the basis of structural connectivity and conductivity patterns of the individual brain, helping to explain observed effects as well as improving the targeting of specific brain areas. On the one hand, computational models can simulate the consequences of neurostimulation and serve as a hypothesis-driven tool linking models with stimulation outcomes [45]. Increasing knowledge about brain connectivity patterns will allow for more precise and multiple-target stimulation, as well as targeting subcortical regions by the means of cortico-subcortical connections, as recently demonstrated for transcranial magnetic stimulation protocols [46]. To this end, viewing the brain as an array of interacting structural and functional ‘networks’ is crucial. Gaining information about these networks will become requisite for future tES studies, especially in the case of tACS where the information about frequency and phase of brain oscillations has been demonstrated to be crucial for the modulation of working memory performance [20**]. Moreover, the possibility to simultaneously interact with multiple nodes of a network is appealing. So far, limits have been set by available technologies allowing for one or two ‘active’ stimulation sites only. However, recent advances in the devices and the modeling of tES-induced electric fields enable multiple-site stimulation [47] and the possibility to trace

complex connectivity patterns, thus orchestrating between and within-network dynamics.

Going forward, the targeted application of tES methods in combination with technologies that have informed the field about the importance of individual differences in the past could further deepen our understanding of such processes, which, in turn, would enable us to design more efficient and tailored cognitive enhancement protocols. This could be achieved by combining tES with individualized current modeling, structural and functional MRI, electroencephalography (EEG), and transcranial magnetic stimulation (TMS). Successful integration of these techniques in addition to a detailed knowledge of genetic and metabolic factors, could not only advance our understanding of how individual brain differences arise, but inform us about how to leverage this knowledge optimally within the context of interventions aimed to enhance human cognition.

Finally, the opportunity to affect ('entrain') brain oscillations by transcranial oscillatory electrical patterns has opened a new era for perturbation-based neuroscience, allowing researchers to causally explore the interaction between brain oscillations and manifested behavior. However, technical challenges need to be addressed and overcome to enable simultaneous stimulation and monitoring of brain activity in the very same location (e.g. amplifiers saturation, presence of stimulation artifacts in the EEG signal, loss of signal of interest when applying notch filters in the case of tACS), as well as reliable gating/triggering of stimulation by ongoing measures of brain activity. Successful advancements in basic science and engineering approaches would for example allow the implementation of closed-loop systems for multifocal, spatially and temporally individualized tES interventions to improve the efficacy of controlled modulation of human cognitive processes.

In conclusion, tES has recently confirmed its role as a powerful tool for cognitive enhancement, with potential benefits for pathological conditions. Recent innovations have led to the design of new tES methods and contributed significantly to the understanding of neurophysiological effects of different tES methods on the brain. Future research will aim to improve cognitive enhancement methods by simultaneously combining a variety of techniques also giving researchers the impression that a more complex and vast scenario is on the horizon. Such complexity just represents a valuable opportunity for the development of finely tuned cognitive enhancement and therapeutic interventions, where tES features, like its portability, will play a fundamental role to bring lab results to a broader public. A future with people wearing portable devices helping them to stay awake during nightshifts or while driving a car, or improving their motor coordination during an intense track and field training

session is relentlessly becoming a more and more plausible and socially accepted scenario. Therefore, more attention to the impact of individual difference on the response to tES and an open, academia-based debate about regulations for tES application should hopefully drive the field hereafter.

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Dr. Pascual-Leone serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectronics, Axilum Robotics, Magstim Inc., and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) and magnetic resonance imaging (MRI). All other authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

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