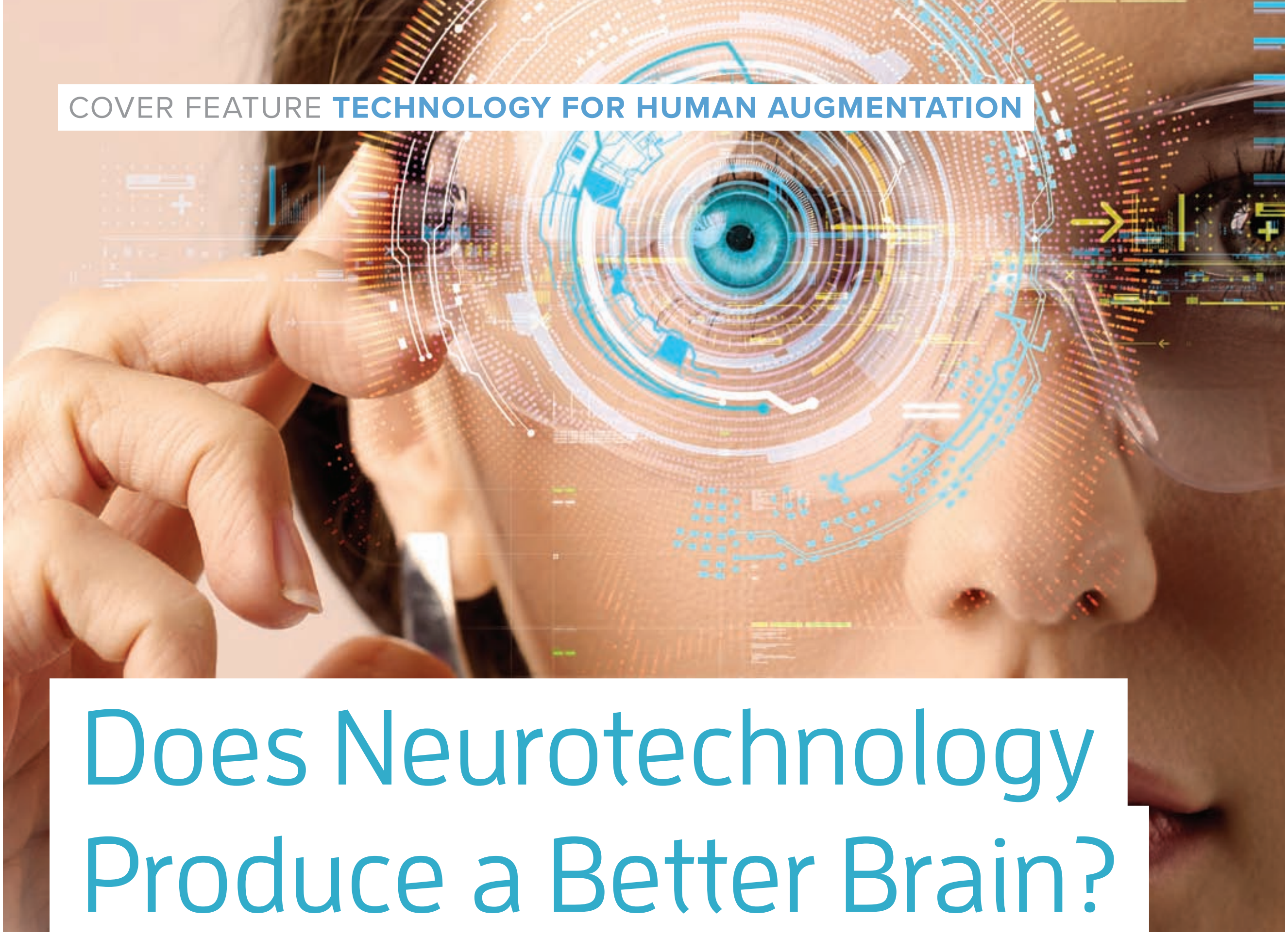

Does Neurotechnology Produce a Better Brain?

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Neurotechnologies in clinical applications can image the brain noninvasively, but they typically require surgical insertion to stimulate it. Although an increasingly popular alternative is to use noninvasive stimulation to enhance nervous system functions, questions about its effectiveness and ethical use remain unanswered.

Noninvasive recording devices that capture and analyze brain and body signals are becoming significantly more affordable as technology moves from the laboratory to practical applications. Users can now monitor their own cognitive fitness or use monitoring results to enhance entertainment, gaming, and physical and procedural training. Science has made large gains in human augmentation through such recording devices,[1] which have tremendous potential for enriching entertainment, enhancing learning, and empowering those with disabilities. For example, neurotechnologies enable communication through external brain–machine interfaces, make it easier for individuals to recall information, and generally improve cognitive performance. Augmented reality devices enhance perception even more by sensing signals outside the human sensory spectrum or field of view[2]—a capability poised to transform activities such as gaming and driving. Two closely related research areas, augmented cognition and neuroergonomics, are focused on sensing and decoding a person's cognitive state in terms of perception, working

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TRANSCRANIAL ELECTRICAL STIMULATION HAS THE POTENTIAL TO EASILY AND INEXPENSIVELY CHANGE BRAIN FUNCTION AND ACCELERATE LEARNING.

memory, and decision making to optimize their ability to process information by adapting information delivery.

Brain–machine interfaces use a variety of brain-recording methods to directly control external devices that facilitate communication. With these devices, users can select letters and words on a screen,[3] decode target locations and trajectories to control a cursor,[4] control robot arms to manipulate objects,[5] and even enable brain-to-brain communication through machines.[6]

At present, neurotechnology can improve cognitive function through brain training or neurostimulation. Brain training changes neural function by presenting challenging tasks to subjects to increase cognitive skills by engaging local and global brain circuits. The goal is to exercise users' new skill levels as they learn, eventually altering their behavior, which enables them to raise their performance ceiling. However, researchers disagree on the extent to which skills learned through brain training transfer or generalize to other daily tasks.[7] In contrast to brain training, neurostimulation alters brain functions directly by external manipulation. Noninvasive neurostimulation applies external electromagnetic, acoustic, or thermal fields to alter the neural tissue's biophysical properties and induce long-term changes in neural plasticity. Neurostimulation takes many forms, but the goal is the same: to alter different neural functions (change brain plasticity) in various brain regions. After a stimulation session, effects can last for minutes, hours, or days. Repeated device use can permanently change the brain's structure and function. To better understand how these complementary neurotechnologies augment the human brain, we explore their potential applications and identify open questions about their use—from their basic science and device design to therapeutic efficacy and ethical application.

UNDERSTANDING TRANSCRANIAL ELECTRICAL STIMULATION

One form of neurostimulation is transcranial electrical stimulation (tES), sometimes referred to as transcranial current stimulation (tCS), which is becoming more widespread because of its potential to easily and inexpensively change brain function and accelerate learning. In the online US National Library of Medicine archive (PubMed), the number of publications with the keyword "tDCS," a popular form of tES that uses direct-current stimulation (DCS), increased from 5 publications in 2000 to 696 publications in 2016.

Although tES has been applied in various settings as part of electrotherapy for centuries, studies that examine the fundamental science behind its effects have been published only in the past two decades, motivated by advances in brain-imaging tools and models.[8] tES devices use electrical currents to modulate neuronal function.

tES devices administer current through electrodes on the scalp, so superficial brain targets—those closer to the scalp—are most accessible with these methods because each electrode's field strength drops off rapidly as brain-tissue depth increases. This field-strength relationship is also a function of individual anatomy and ongoing, endogenous brain activity. The use of higher resolution structural neuroimaging and electrodes with a higher density might increase targeting precision.

Researchers are employing neuroimaging and electromagnetic field modeling to determine the exact neural mechanisms by which tES effects changes in the brain. The general assumption is that tDCS increases neuronal excitability with anodal stimulation and decreases excitability with cathodal stimulation. However, recent modeling work has shown different effects on different types (excitatory or inhibitory), orientations (radial or tangential), and parts of a neuron (axons, dendrites, and soma). No current study has conclusively identified how tDCS modifies neurons and circuits in primates, although experiments with rodents and ex vivo brain slices has revealed some of these effects in circuits and single neurons. Overall, researchers disagree about tES's effectiveness.[9]

CHALLENGES OF NONINVASIVE SENSING

Perhaps the greatest challenge of noninvasive neurostimulation is inferring causal relationships between behavior and measured brain activity.[10] Brain complexity must be considered at each of the levels shown in Figure 1a. At the regional level are activity patterns within a functional network of brain areas. Connectivity between areas mediates communication dynamics at the cell assembly level. At the column level, spatially grouped columns show increased neuronal interconnections and response properties in a particular structure, such as the visual cortex. Networks of neurons exist in well-defined computational circuits, such as a cortical stripe. Finally, at the neuron level,

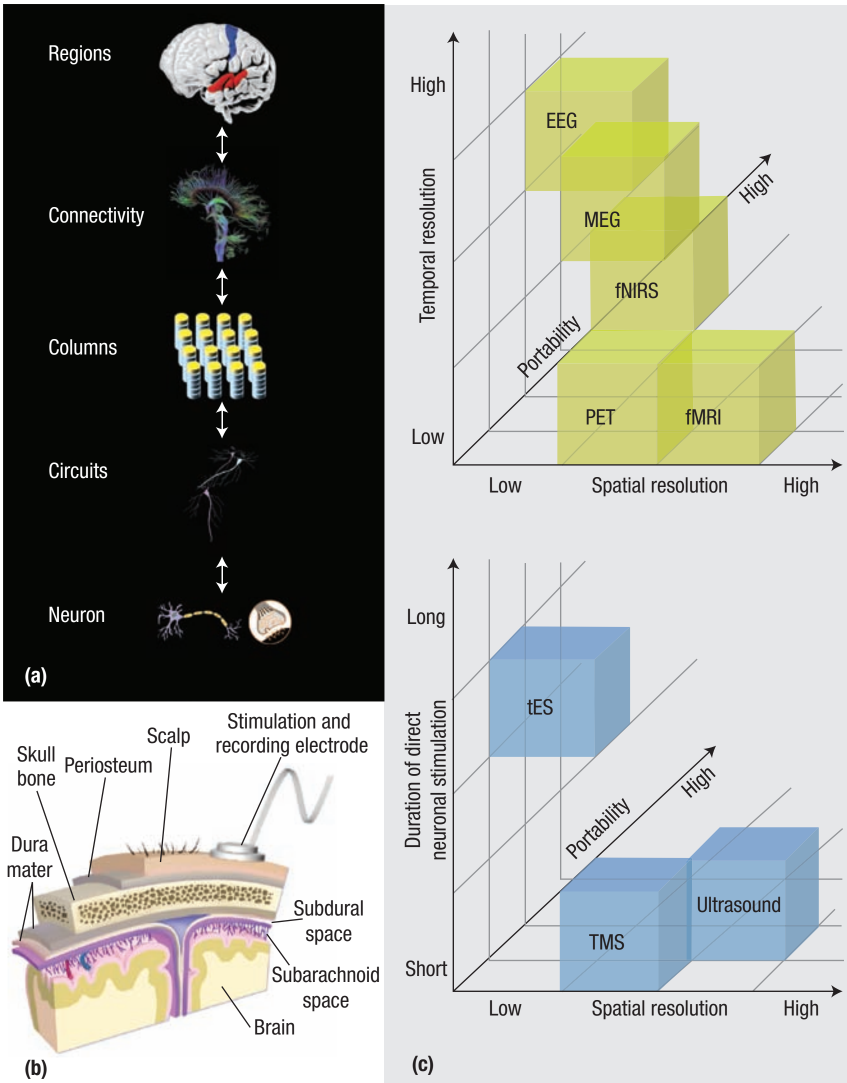


FIGURE 1. Observations of brain complexity. (a) Observed levels range from neuronal to regional. (b) Noninvasive sensors must penetrate different tissues to sense and stimulate areas of interest in the brain. Electrical, magnetic, and hemodynamic sensing must remove all spatial and temporal artifacts introduced by intervening layers above the brain tissue (skull, skin, and so on). (c) Sensing and stimulation techniques have different spatial and temporal sampling and portability profiles. EEG: electroencephalography; MEG: magnetoencephalography; fNIRS: functional near-infrared spectroscopy; PET: positron emission tomography (radiation or nuclear medicine imaging to produce 3D images of body functions); fMRI: functional magnetic resonance imaging; tES: transcranial electrical stimulation; TMS: transcranial magnetic stimulation.

intracellular structures and molecular mechanisms compute information, such as intradendritic processing and receptor-expression pathways.

Figure 1b shows a cutaway view of the skull and sensors in noninvasive recordings—where sensors detect the signatures of neural activity from the scalp after the signals pass through multiple tissue types. These signals can be "smeared" in all three spatial dimensions and corrupted by nonneural signal sources such as muscle tissue or blood. In computational terms, these artifacts comprise a complex filtering process with both active and passive elements—filtering that poses an important challenge in measuring brain activity. Because of this signal contamination, the neural activities of individual neurons and circuits (spikes and local field potentials) are not easy to quantify or reconstruct. Noninvasive sensing incorporates signal-processing techniques and algorithms to remove noise from sensor data, reduce dimensionality, and reconstruct the sources of neural activities.

As shown in Figure 1c, each technique has different spatial and temporal sampling and portability profiles. Electromagnetic sensing methods, such as electroencephelography (EEG) and magnetoencephalography (MEG), measure primary activity by sensing fields from neural activity. Secondary activity such as brain metabolism can be recorded noninvasively at the scalp with two techniques. Functional near-infrared spectroscopy (fNIRS) measures the uptake of blood oxygen using highly portable and inexpensive infrared light sources and detectors. Functional magnetic resonance imaging (fMRI) measures the uptake of blood oxygen using a large and typically expensive MRI machine to record changes in the hemoglobin's magnetic susceptibility.

IMPROVING COGNITIVE FUNCTIONS

Research has emphasized the application of neuroaugmentation to modify and potentially improve basic cognitive functions primarily because experimental paradigms are stable and there is consensus on a basic understanding of how these systems operate. Working memory, one of the most widely studied cognitive functions, is a critical cognitive primitive in attention selection, reasoning, memory and decision making and involves temporarily storing and manipulating information. Figure 2a gives a flavor of regional diversity and complexity, and Figure 2b compiles results from studies that have

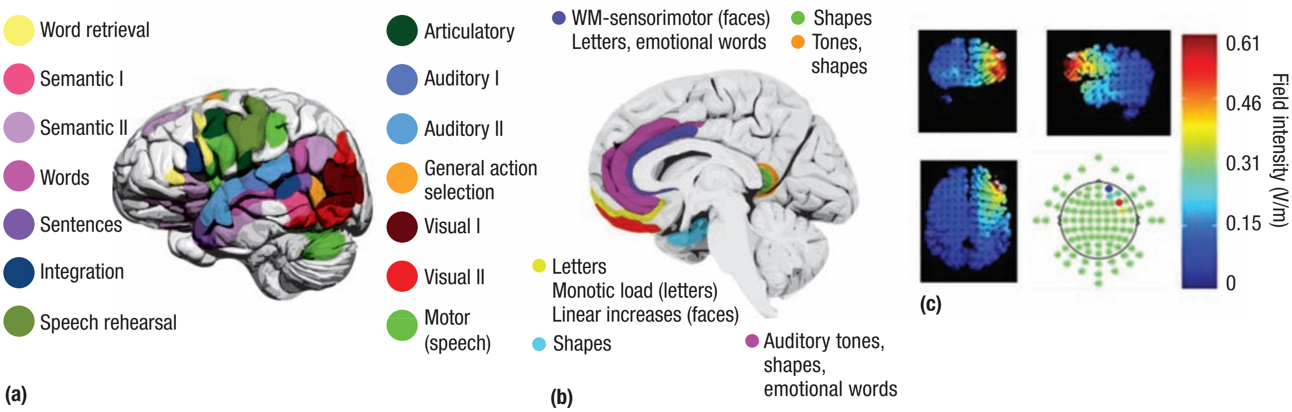


FIGURE 2. Functional activity evoked in the brain, and models for targeted stimulation. (a) Neural activity for general cognitive processes across the cortical surface. (b) Interior view of the brain and regions evoked by different working memory tasks that are important to everyday cognition. In (a) and (b), designations are for the *N*-back task unless otherwise specified. (c) A finite-element model (FEM) is used to optimize the tES targeting of a defined brain region—in this case, the right dorsolateral prefrontal cortex (rDLPFC), which is a primary region involved in executive function and working memory (WM)—using a maximum focality montage, with fields shown on different brain orientations and montage shown on the lower right in the 10–20 electrode system.

documented significant brain activity across the brain during working memory performance.[11]

To improve these functions, noninvasive stimulation must target the associated regions by delivering current through electrode montages. Computational simulations are used to design montages for reaching deep-brain structures and can trade off field intensity or montage complexity to enhance focality. Figure 2c shows a sample optimization with a finite-element model (FEM) used to simulate the fields from such a montage design.

Researchers typically assess working memory performance in terms of the *N*-back task—a continuously performed task in which the subject is given a sequence of images and asked to identify a match within that sequence. A 1-back is a comparison of the current stimulus or image with the last one presented, a 2-back is a comparison with the image presented two images ago, and so on. Stimulation of the dorsolateral prefrontal cortex (DLPFC) has been linked to improvements in basic cognitive functions, including working memory in performing the *N*-back task.[12]

However, evidence of improvement varies widely across methods and studies. One study shows a repetitive transcranial magnetic stimulation (rTMS) technique applied to the DLPFC in *N*-back task performance improves the percentage of correct responses and shortens reaction times, whereas another study reports tDCS improves only reaction times.[13] Even more puzzling, authors of a recent metastudy concluded that tDCS has no net effect on any of these cognitive measures.[14] Clearly, more research is needed to resolve these disparate studies of neuroaugmentation methods and to move current understanding beyond basic mechanisms. This understanding is a prerequisite to reproducing these methods and optimizing their effectiveness.

Language acquisition

Despite these contradictions, studies show that DLPFC stimulation improves working memory and thus could be the basis for enhancing higher cognitive functions, such as language acquisition. Noninvasive neurostimulation technologies are particularly well suited to modulate specific brain functions that are near the cortical surface. Learning rate is a critical measure for complex cognitive functions such as language and skill acquisition, and the ability to increase that rate depends heavily on the stimulation technique's spatial and temporal characteristics. Several regional networks are activated in language acquisition, which combines speech production and comprehension and semantic and lexical comprehension. Executing these tasks involves multiple distributed brain areas and networks, including those involved in working memory, as well as focal regions, such as Broca's and Wernicke's areas (two regions intimately involved in language production and perception, respectively). Studies show that language production and verbal working memory share a neural substrate, and using tDCS on this substrate can increase language learning rate and the successful acquisition of new words.[15]

Complex skill acquisition

Although research has produced sufficient evidence that neurostimulation technologies can effectively augment basic cognitive functions, such as working memory, the extent to which these augmented skills generalize to real-world tasks such as learning complex and novel procedures has yet to be determined. Examples include flying an aircraft, which requires learning multiple motor, decision-making, and perceptual skills and fusing them effectively, and detecting camouflaged

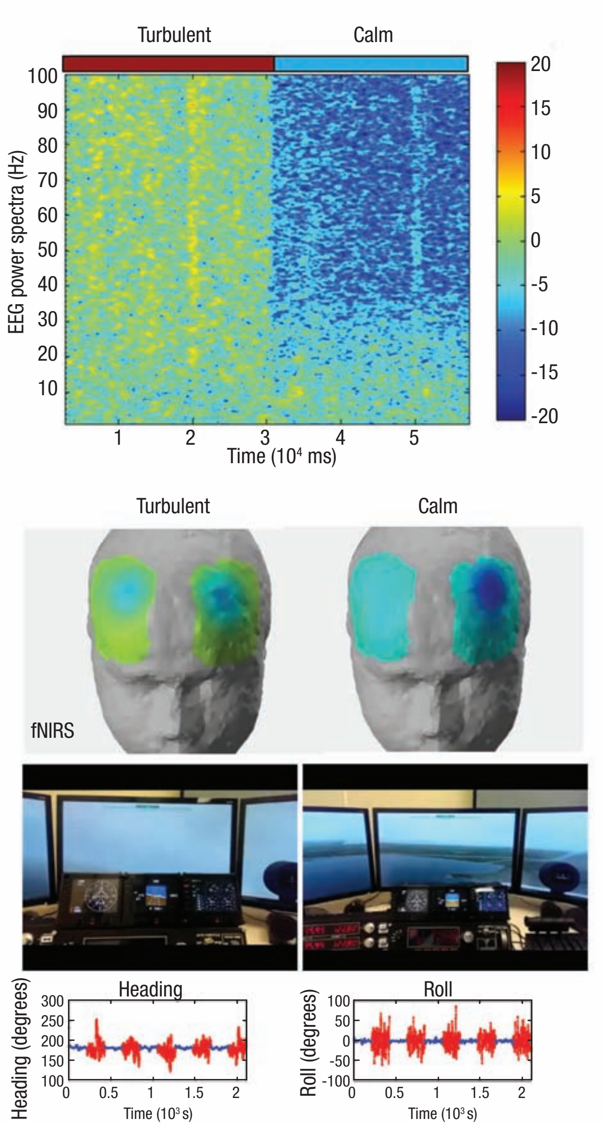


FIGURE 3. Using tDCS, a popular form of tES that uses direct-current stimulation (DCS), to modulate a subject's ability to learn how to land an aircraft using a flight simulator. During flight control under turbulent weather conditions, neuroimaging of the bilateral DLPFC with EEG (spectrum after weighting with independent component analysis) showed a significant increase in broadband spectral power in the frontal cortex. Neuroimaging with fNIRS taken simultaneously with the EEG showed an increase in hemoglobin concentration. Heading and roll were control inputs given during turbulent trails (red) and calm trials (blue).

objects, which requires visual perceptual learning.

Piloting an aircraft. To better understand how neurostimulation can accelerate the learning of complex skills, we conducted a study in which we applied tDCS to the DLPFC of healthy subjects whom we instructed to learn aircraft piloting through a flight simulator. We evaluated the ability of two groups of subjects to land an aircraft using the Beechcraft Baron B-58 X-Plane simulator. For one group, we applied 2 mA of stimulation using tDCS; the other group had the same task but we gave them a sham protocol. The sham protocol group received the sensation of stimulation as the tDCS protocol ramped up but not the actual stimulation.

We took measurements for five flight-control trials, in conditions ranging from calm to turbulent, over four consecutive days.[16] We used EEG to record both electrical potentials and simultaneously measured hemodynamic metabolism using fNIRS. We then evaluated function changes in brain activity during the four days of flight learning. Figure 3 shows the results showed of maintaining level aircraft flight in turbulent weather—wind set to 10 knots and turbulence to 10 percent—and in calm weather. Our findings point to a characteristic signature of cognitive workload during flight, which reflects the subject's engagement and effort in maintaining level flight.

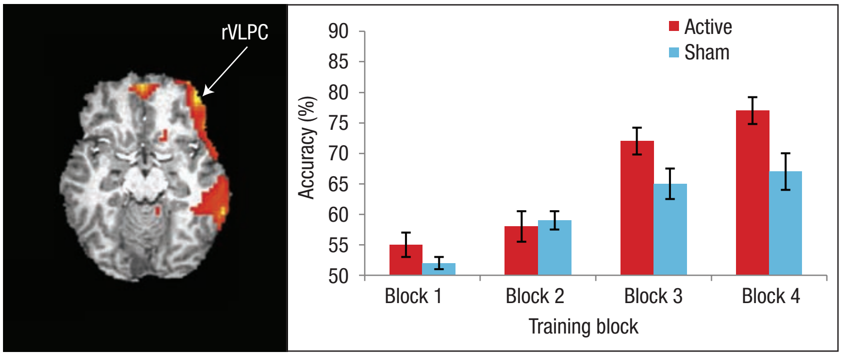
tDCS facilitated an increase in learned skill consistency for piloting an aircraft to a successful landing, as measured by the G-force on the runway at touchdown, compared with the group that received a sham stimulation.[16] This demonstration of real-world skill learning with neurostimulation shows that these methods might have application beyond the laboratory and standard psychological testing and might be suitable in classroom and training environments to accelerate learning and enhance task performance.

Additional studies are needed to test neurostimulation methods in more domains and applications. One area of concern is skill retention, which can be addressed by conducting longitudinal follow-up studies to our piloting experiment to test how long subjects can retain their newly acquired skills.

Detecting camouflaged objects. In 2012, Vince Clark and his colleagues at the University of New Mexico conducted a seminal study of performance augmentation with tDCS, reporting that subjects exhibited considerable improvement in their ability to detect camouflaged objects after only 30 minutes of 2-mA anodal tDCS directed at their right ventrolateral prefrontal cortex (rVLPFC).[17] The assigned task was to detect camouflaged objects hidden in a computerized virtual environment based on DARWARS Ambush!, a simulator that has been used to train military personnel deploying in the Middle East. Researchers determined the target area (the right VLPFC) using neuroimaging findings from a separate study that investigated differences in hemodynamic response among subjects with different expertise levels in camouflaged object detection. Figure 4a shows the results of the 2012 study.

Using fMRI, Clark's group identified a set of key regions in subjects at intermediate learning stages, but not in novices. Some of these areas included the right parietal cortex, an area involved in visual attention; the medial prefrontal cortex, an area implemented in action monitoring; the parahippocampal gyrus, an area involved in learning and memory, and the right VPFC, an area linked with the cognitive control of attention and working memory. In subsequent studies, the group then applied tDCS to the superficial cortical regions they identified. tDCS directed at the right VLPFC and right parietal cortex resulted in a pronounced increase in task performance, as shown in Figure 4b.

A few studies have validated these results, highlighting the robustness of tDCS guided by neuroimaging. One study showed a correlation between the enhancement of object detection and attention with tDCS on the right VLPFC,[18] which demonstrates the efficacy of neuroimaging-guided brain stimulation. However, replication studies are few and far between in tDCS research, despite recent demand for them.



(a) (b)

FIGURE 4. Selected neuroimaging findings and behavioral effects of applying 30 minutes of 2-mA anodal tDCS to the right ventrolateral prefrontal cortex (rVLPFC) of subjects aiming to detect camouflaged objects. (a) F-statistic map showing the enhanced blood oxygenation level dependent (BOLD) response in the rVLPFC when comparing cue-related activity (cue versus no-cue) between subjects at the novice and intermediate levels of camouflaged object detection. (b) Object detection accuracy over four training blocks for the 12 subjects given active stimulation (red) and the 23 subjects given sham stimulation (blue). Error bars represent standard error.

AUGMENTING MOTOR SKILLS

Numerous groups have demonstrated the effectiveness of neurostimulation in augmenting motor skills and replicated the results of early work of pioneering laboratories. Investigations into motor learning have reported that tDCS enhanced total motor-skill acquisition over multiple days and bolstered subjects' strength, dexterity, and exercise efficiency. However, as is true of many neuromodulation studies, results vary considerably across studies. One study shows that up to half the subjects can be nonresponsive in an experiment applying tDCS to the primary motor cortex.[19] Other studies have observed correlations in opposite directions between the current, current density, and response effect size with tDCS-induced motor and visual-motor learning.[20] The commercial use of tDCS to enhance motor skills requires additional studies focused on retention; only a few such efforts have been published.[21–23]

NEUROTECHNOLOGY MARKET DRIVERS

Despite unanswered questions about its effects, tES remains the most common form of neurostimulation. It even has a community of do-it-yourself users (www.diytdcs.com) and received a writeup in *The New Yorker*.[8]

As part of our investigation into neurotechnology's science and challenges, we identified several drivers in the commercial growth of tES and of neurotechnology in general, including the current regulatory climate and the devices' simplicity, affordable cost, and usability.

Regulation and device characteristics

The clinical device marketplace requires large investments for certification and approval through the US Food and Drug Administration (FDA). Examples of these large-scale efforts include work to improve motor skills in patients with Parkinson's disease through invasive neurostimulation, such as deep-brain stimulation, and noninvasive neurostimulation, such as tDCS.

However, the FDA does not regulate *nonclinical* tES technology, for which there is a robust marketplace with companies targeting basic research and consumer use for neuroaugmentation. Consumer devices typically comprise electrodes applied to the scalp or forehead connected to stimulating electrodes that are linked to an interface controller. tES devices have many of the same device characteristics and design challenges that are common in noninvasive neural recording technology. Much of the basic technology in the current market was fostered by decades of early investments by companies investigating the brain for field applications by agencies such as DARPA.

Consumer devices in the neural recording marketplace are maturing rapidly, primarily because of their early application in gaming. In addition, conferences such as Experiential Technology (XTech; www.nerogaming-conf.com) are well attended. Health-related monitoring and neuroaugmentation for activities such as meditation are also popular uses of neural recording devices.

The consumer neurotechnology market continues to expand, though critical issues remain, such as substantiating signals recorded using the easy-to-use dry electrode technologies.

THE EXTENT OF NEUROTECHNOLOGY'S USABILITY DEPENDS LARGELY ON THE DEVICE, APPLICATION, AND USER'S EXPERIENCE.

Usability and applications

The extent of neurotechnology's usability depends largely on the device, application, and user's experience. A decade ago, neural recording was done primarily in the laboratory with a trained technician, who applied the sensors, calibrated the recording device, and monitored signal quality while the subject was engaged in a task. Current devices can be applied by their users with minimal calibration. In most tES devices, for example, automated impedance measurements are built in for safety. However, researchers are only beginning to understand the effects of this technology, which raises important questions for the consumer:

- Will the device actually change my brain?
- How complicated is it, and how long does it take to calibrate?
- How important is electrode placement, and what are the consequences of misplacement?
- How often do I have to use it to get the desired augmentation effect?
- How do effects change across devices?
- Will the device have the same effects on another person?

Design considerations. Neurotechnology applications are no longer confined to stationary indoor settings such as gaming consoles. However, moving to mobile applications introduces new design considerations, such as environmental, user, and activity conditions. The device designers must now consider temperature and humidity; the user's sweat and oil, which can affect electrode impedance at the tissue interfaces; and any movement that changes the interface and signal quality. Most wireless tES devices are battery-powered, light, and small enough to already be suitable for outdoor use. Future devices might be used during extended activities, such as military scenarios that require intermittent application for days without access to infrastructure. These devices must be durable and consume power efficiently.[24]

Application drivers. Research on noninvasive brain stimulation is abundant. tES research has also flourished in the past several decades, with clinical applications in the treatment of depression, Parkinson's disease, and stroke, as well as cognitive applications in working memory, motor learning, visual-perceptual learning, simple somatosensory and visual-motion perception learning, and memory. The effects of tDCS on cognitive augmentation can be particularly pronounced, with enhancements of nearly a full standard deviation.[12] The size of these effects is expected to increase, as new protocols and hardware are developed to enhance the resolution and reliability of stimulation. Additionally, new devices combine tDCS, EEG, and fNIRS in a single closed-loop system, which enables simultaneous brain monitoring and stimulation.[16] Such developments will broaden the use of noninvasive brain stimulation and add to the already considerable number of augmentation applications.

OPEN QUESTIONS

Although many studies have demonstrated the efficacy of neuroaugmentation technologies across several practical and functional domains, numerous questions and critical factors must be answered before experimental results can translate into mainstream technologies for work and home environments. Practical constraints and limits for both sensing and stimulation devices go beyond typical size, weight, power, and cost considerations for wearable sensors and devices. Designers of neuroaugmentation devices for military use, for example, must consider the extreme environmental range and durability required in combat applications, device fit across individuals, and physical concerns such as an individual's sweat level and hair length and any clothing or movement constraints.

Figure 5 shows a potential application that meets these requirements. Sensed biological data would integrate with the stimulation paradigm so that neuroaugmentation would be applied only when the particular individual needs it. Such adaptive intervention would be based on personalized individual neurophysiological states and emerging task requirements.

Many problems must be solved before we can realize such applications. One challenge is the choice of methodology and the creation of protocols and parameters to plan and guide neuroaugmentation. For example, how long does it take to measure or modulate the desired physiology or behavior? There is also no consensus on the optimal dose of neuromodulation or the amount of time that its benefits persist. Approximately one year is the longest reported period to date. The reliability and effectiveness of neural measures and doses, and when should they should be applied or ceased, are also not well understood. Additional studies are needed to define an effective measurement process and ways to assess progress toward the target physiological or behavioral state, relative to sham effects. Finally, the risks of continuously using neuroaugmentation on long-term health have yet to be determined. Significant time and resources are required to conduct and replicate risk studies to develop treatments into a marketable therapy.

Despite these obstacles, the future of neuroaugmentation technologies looks bright. Current advances in wearable sensors and devices, personalized medicine, and tailorable models are likely to accelerate research in understanding the scope of neuroaugmentation tools and their impact on performance, learning, and training. With this understanding, designers can produce an adaptable system of multiple wearable sensors and modulation devices. The application of such a system will be limited only by our understanding of the biological, cognitive, and physical processes that underlie human performance. **C**

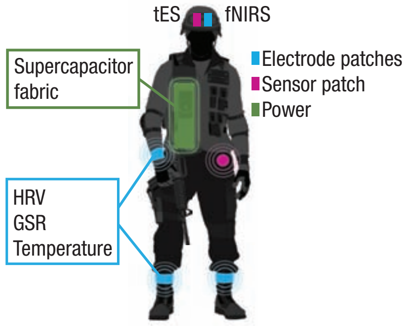


FIGURE 5. An overview of potential sensor and stimulation packages in a military application. Portable devices across the body will enhance various neurological functions. tDCS for working memory, focus, enhanced learning, and stress mitigation; fNIRS for neurophysiological sensing; and heart-rate variability (HRV) and galvanic skin response (GSR) for sensing physiological biomarkers.

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ADDITIONAL READING

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