Neuroenhancement in Military Personnel: Conceptual and Methodological Promises and Challenges

Tad T. Brunyé
U.S. Army DEVCOM
Soldier Center
Natick, MA
UNITED STATES OF AMERICA

Thaddeus.t.Brunye.civ@mail.mil

Monique E. Beaudoin
Applied Research Laboratory for
Intelligence and Security
College Park, MD
UNITED STATES OF AMERICA

MoniqueB@umd.edu

Kathryn A. Feltman
U.S. Army Aeromedical
Research Laboratory
Fort Rucker, AL
UNITED STATES OF AMERICA

Kathryn.a.Feltman.civ@mail.mil

Kristin J. Heaton
U.S. Army Research Institute of
Environmental Medicine
Natick, MA
UNITED STATES OF AMERICA

Kristin.j.Heaton.civ@mail.mil

Richard A. McKinley
U.S. Air Force Research
Laboratory, Wright-Patterson Air
Force Base, Dayton, OH
UNITED STATES OF AMERICA

Richard.McKinley.2@us.af.mil

Oshin Vartanian
Defence Research and Development
Canada, Toronto Research Centre
Toronto, ON
CANADA

Oshin.Vartanian@drdc-rddc.gc.ca

John F. Tangney
U.S. Office of Naval Research,
Arlington, VA
UNITED STATES OF AMERICA

John.f.Tangney@navy.mil

Jan Van Erp
Netherlands Organization for
Applied Scientific Research (TNO),
Soesterberg
THE NETHERLANDS

Jan.VanErp@tno.nl

Annika Vergin
Planning Office of the Bundeswehr,
Federal Ministry of Defense
Berlin
GERMANY

AnnikaVergin@bundeswehr.org

Arcangelo Merla
University G. D'Annunzio of Chieti-Pescara, Institute for
Advanced Biomedical Technologies, Department of
Neuroscience, Imaging and Clinical Sciences, Chieti
ITALY

A.Merla@next2u-solutions.com

Annalise Whittaker
Defense Science and Technology Laboratory, UK
Ministry of Defense, Salisbury
UNITED KINGDOM

AhWhittaker@mail.dstl.gov.uk

ABSTRACT

Military personnel are subjected to prolonged operations in harsh and undesirable conditions characterized by severe environmental exposures, resource scarcity, and physical and mental encumbrance. Prolonged military operations under these conditions can degrade the already limited perceptual, cognitive, and emotional resources necessary to sustain performance on mission-related tasks. The complex multi-domain operations of the future battlespace are expected to further increase demands at even the lowest levels of the military echelon. These demands will be characterized with increasingly prolonged operations of small units in austere environments with limited resupply and degraded technological capabilities. It is therefore critical to identify new training and technological approaches to enable sustained, optimized, and/or enhanced performance of military personnel. Research in the international defence science community, academia, and industry has developed several promising neuroscientific strategies for pursuing this goal, including *neuromodulatory and neurofeedback techniques. The present paper reviews the state of the art in cognitive neuroenhancement research and development from six participating nations: Canada, Germany, Italy, The Netherlands, United Kingdom, and the United States of America. Six neuromodulation techniques are reviewed, including transcranial magnetic stimulation (TMS), transcranial focused ultrasound stimulation (tFUS), transcranial electrical stimulation (tES), transcutaneous peripheral nerve stimulation (tPNS), photobiomodulation, and cranial electrotherapy stimulation (CES). Three neurofeedback techniques are considered, including the use of electroencephalography (EEG), functional magnetic resonance imaging (fMRI), and functional near-infrared spectroscopy (fNIRS) for monitoring brain states, with feedback loops enabled through machine learning and artificial intelligence. Participating nations summarize basic and applied research leveraging one or more of these neuromodulation and neurofeedback technologies for the purposes of enhancing Warfighter cognitive performance. The report continues by detailing the inherent methodological challenges of cognitive neuroenhancement and other considerations for conducting research, development, and engineering in this domain. The report concludes with a discussion of promising future directions in neuroenhancement, including biosensing, improved mechanistic and predictive modelling and software tools, developing non-invasive forms of deep-brain stimulation, testing emerging theoretical models of brain and behavior, and developing closed-loop neuroenhancement and human-machine teaming methods. Emphasis is placed on the conceptual and methodological promises and challenges associated with planning, executing, and interpreting neuroenhancement research and development efforts in the context of Warfighter selection, training, operations, and recovery.*

Keywords: perception, cognition, cognitive neuroscience, neuroenhancement, human performance, transcranial magnetic stimulation, transcranial electrical stimulation, transcutaneous peripheral nerve stimulation, transcranial focused ultrasound, cranial electrotherapy stimulation, photobiomodulation, electroencephalography, functional magnetic resonance imaging, machine learning, artificial intelligence, biosensing, human-machine teaming, neurofeedback

1.0 PURPOSE AND OBJECTIVE

Cognitive neuroenhancement tools and techniques hold potential to increase mental capacity and revolutionize the effectiveness and efficiency of military personnel engaged in demanding operational tasks. Academic, defense, and industry research and development efforts have resulted in several cognitive neuroenhancement technologies with highly varied effectiveness, reliability, safety profiles, and readiness levels for military application.

The NATO Human Factors and Medicine panel activity titled Cognitive Neuroenhancement: Techniques and Technology (HFM-311) was organized to collate and examine the state-of-the-art research, techniques, and technologies in cognitive neuroenhancement including (but not limited to) neuromodulation and neurofeedback. The group reports on recent research and development efforts, lessons learned, strengths and weaknesses (including undesirable side effects) of each approach and combinations of approaches, best practices among the NATO participants, scientific/technological challenges, and other important considerations for eventual deployment of neuroenhancement technologies to training and operations.

The objective of this report is to summarize research activities and scientific perspectives of the HFM-311 group, with an emphasis on some of the successes and inherent challenges associated with cognitive performance enhancement, optimized readiness and resilience, and accelerated recovery and reset.

2.0 INTRODUCTION

Neuroenhancement involves the application of neuroscience-based techniques and technologies to alter central and/or peripheral nervous system activity and enhance mental function [1], [2]. Mental functions are diverse and dynamic and include the brain mechanisms and processes involved in perception, cognition, and emotion. Enhancement is distinct from optimization. Enhancement involves accelerating or amplifying individual and/or team performance beyond peak capability, whereas optimization involves maintaining peak performance in the face of adversity [3]. Herein we consider two specific forms of neuroenhancement: neuromodulation and neurofeedback.

3.0 NEUROMODULATION

Neuromodulation involves introducing exogenous energy into the central or peripheral nervous system to alter nervous system activity, neurotransmitter and hormonal activity, and affect and behavior. Across participating NATO countries, five primary methods of neuromodulation have been considered: transcranial magnetic stimulation (TMS), transcranial electrical stimulation (tES), transcranial focused ultrasound stimulation (TFUS), transcutaneous peripheral nerve stimulation (TPNS), and cranial electrotheraphy stimulation (CES).

3.1 Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation (TMS) uses time-varying magnetic fields to generate a powerful electrical field in the brain through the process of electromagnetic induction, resulting in suprathreshold modulation of neuronal activity [4].

The ability to alter rTMS parameters to reliably inhibit or excite neural circuitry suggests its potential value for selectively altering cortical activity to enhance cognitive performance [5]. Furthermore, the ability to target relatively medial brain regions critically involved in a multitude of cognitive processes, such as the medial prefrontal cortex, insula, and anterior cingulate cortex, presents exciting opportunities for modulating a range of perceptual, cognitive, and affective processes relevant to military operations. These include the ability to quickly detect and discriminate threats, comprehend information, solve problems and make decisions, and regulate emotional responding under conditions of stress and adversity.

A review of TMS and rTMS for cognitive enhancement applications revealed sixty-one published papers suggesting enhancement of a broad range of processes including “perceptual discrimination and motor learning, faster eye movements, speeded visual search and object identification, and superior performance on tasks involved in attention, memory, and language,” [5]. In that review, the authors speak to three classes of potential enhancement mechanisms with TMS: non-specific effects, direct effects, and addition-by-subtraction.

Non-specific effects pertain to psychological effects of the stimulation methodology that are not due to any direct influence of the induced electromagnetic field. Specifically, intersensory facilitation and arousal due to the vibration and clicking of the TMS device can enhance performance on concurrent (or even offline) tasks [6]. In forthcoming sections, it will be noted that non-specific effects of neuromodulation also pervade other stimulation methods.

Direct effects pertain to stimulation-induced effects on brain regions ostensibly involved in the successful performance of a cognitive task. Direct effects of brain stimulation on cognitive task performance have been found with both offline (prior to task performance) and online (during task performance) protocols. For example, offline excitatory rTMS targeting the left dorsal premotor cortex can reduce movement errors and enhance new motor skill consolidation [7]. Similarly, online excitatory rTMS targeting the parietal cortex can reduce response times during a spatial working memory task [8].

Addition-by-subtraction [5], also termed enhancement through diminishment [9], pertains to attempts to interfere with the function of brain regions that are less essential or counter-productive to task performance. By suppressing the activity of one or more nodes in a functional brain network, researchers can indirectly upregulate the function of a task-critical brain region. Such a pattern could emerge for a variety of reasons, including a release from the inhibitory effects of one node upon another [10], the freeing up of metabolic resources for a critical node [11], or degrading automatic processes that are not essential to learning or task performance [12], [13].

Thus, there is evidence that TMS can induce cognitive performance enhancement through at least three mechanisms, lending support for TMS in military applications. Potential applications include accelerating knowledge acquisition, facilitating memory retention or retrieval, or accelerating motor skill training. Given the size and limited portability of TMS devices, and the need for highly trained technicians for its proper operation, TMS may be most suitable for military educational and training contexts. It may also be suitable for accelerating recovery from traumatic event exposure.

For instance, military personnel are required to learn several general and specialized motor skills, including patterns of whole-body movement (e.g., tactical maneuvering, preparation for aiming, coordinated movement during load carriage), and fine and gross motor skills (e.g., weapon handling, vehicle and aircraft piloting, equipment rigging). Training of complex motor skills is typically conducted at or close to a training facility and may thus be amenable to the introduction of TMS for accelerating the acquisition of new motor skills. A series of studies from the Saitama Medical University (Japan) suggests that rTMS targeting the ipsilateral primary motor cortex can improve motor skill learning [14]–[16]. These results are considered an example of the addition-by-subtraction mechanism, with a release from contralaterally-sourced interhemispheric inhibition facilitating ipsilateral-dependent processes, and could have direct application to military training.

There are at least five challenges associated with the successful adoption of TMS (or rTMS) in military training settings. First, TMS devices will pose prohibitively expensive to purchase, training to operate, and maintenance costs for most military units. Second, TMS administration involves the employment of trained and certified specialists to ensure appropriate system targeting and use. Third, while many of the cited reports offer compelling evidence for potential performance-enhancing effects of TMS, there are also many studies demonstrating that slight and ill-defined changes in stimulation parameters (e.g., location, coil type, frequency, intensity, duration, timing) can reduce or even reverse expected stimulation effects. Fourth, we found no compelling evidence that any learning or training acceleration induced by TMS is maintained over the long-term and/or transferred to similar but unlearned tasks. Indeed, TMS effects on the brain are highly transient; even with high frequency rTMS any neural effects are limited to approximately 1 hour after stimulation. Finally, while TMS is very unlikely to induce harm to brain tissue at typical charge densities (≤ 40μC/cm3/phase), TMS can induce rare but sometimes serious side effects such as headache, seizure, and hearing loss [17].

3.2 Transcranial Electrical Stimulation (TES)

Transcranial Electrical Stimulation (tES) uses direct or alternating current to create diffuse electrical fields on the brain, resulting in subthreshold modulation of neuronal membrane potentials. There are three primary approaches to tES administration: transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS). A relatively recent advancement combines tACS with a direct current (DC) offset to create oscillatory tDCS (osc-tDCS).

A multitude of parameters is manipulated in tES, including characteristics of the electrodes themselves (e.g., surface area, shape, number), the arrangement of electrodes on the scalp, and the frequency, polarity, intensity, timing and duration of stimulation. Each of these parameters has been demonstrated to modulate the robustness and/or reliability of tES effects on brain function and/or behavioral outcomes [18]–[22].

The ability to induce subthreshold modulation of neuronal potential and prime or entrain populations of neurons suggests the potential value of tES for coarsely modulating cortical activity and enhancing cognitive performance [23], [24]. While tES is thought to primarily modulate relatively superficial cortical layers [25], [26], many critical nodes of distributed neural networks are positioned in relatively superficial regions, such as nodes of the frontoparietal control network, default mode network, and dorsal attention network [27]. These networks are responsible for diverse perceptual, cognitive, and affective processes, suggesting that modulating nodes of these networks will carry diverse downstream neuronal, and even behavioral, effects.

Several reviews have been published [23], [24], [28] detailing the potential utility and limitations of tES for cognitive performance enhancement. These reviews largely arrive at the following conclusions. First, many well-designed and high-powered experiments demonstrate positive effects of tES on a range of cognitive tasks. Second, meta-analytic approaches to understanding tES effects on cognitive performance, such as vigilance, working memory, or executive function, find mixed results [19], [29]–[34]. Third, experimental methodologies are highly varied and may underlie disparate tES effects on cognitive performance. Research examining tES effects on cognitive functions uses myriad parameters, including the stimulation devices themselves, electrode type and quantity, stimulation polarity, intensity, and duration, and online versus offline stimulation [35]–[37]. Fourth, the research community lacks a generally accepted mechanistic theory to account for tES effects on brain and behavior. Many theories have been proposed to detail the molecular, cellular, and electrophysiological effects of tES, and how they might link to improvement in behavioral function [38], but each model is only able to account for a portion of extant tES research findings, pointing to a need for more comprehensive mechanistic understandings through experimentation and computational modeling. Fifth, combining tES with other enhancement interventions, such as pharmaceuticals, exercise and cognitive training, is an exciting yet under-researched topic [39].

Thus, there is some evidence that tES can alter cognitive performance, though the effect sizes are small to moderate, and results are highly heterogeneous across studies and laboratories. There are several challenges associated with the successful adoption of tES in military training or operational settings.

First, extant research has not shown consistent or compelling enough results regarding the influence of tES on cognitive performance to warrant near-term adoption in non-research settings; in many cases, tES may prove ineffective at modulating behavior, and at worse it could significantly degrade performance [40]–[44]. Second, long-term safety and sensitization profiles are unknown, with a risk that long-term, repeated use of tES may induce unknown effects on brain structure, function, and disease [45]. Any such risk may be compounded by intensity or duration increases that might result from neuronal desensitization to repeated tES. Third, while many consumer-grade devices are becoming available on the open market, the vast majority of tES research uses research- and/or clinical-grade devices that conform to higher manufacturing and regulatory guidelines. Thus, without compelling scientific data demonstrating the reliability and robustness of effects induced by consumer-grade devices, their adoption is premature and potentially dangerous [46]–[48]. Fourth, no formal clinical certifications exist for safely and reliably preparing and administering tES protocols, introducing the risk that tES administration will suffer from high heterogeneity, poor quality control and reliability, and unintended and potentially dangerous outcomes such as skin irritation, electrical burns, headaches and migraines [45].

Challenges notwithstanding, the international military community has begun adopting tES in research and training settings. In the United States, the Army, Air Force, and Navy have published extensively on the topic of tES for performance enhancement, acknowledging both potential gains associated with its acute and prolonged administration during laboratory tasks, and the many challenges associated with its future application to training and operations [3], [41], [49]–[60].

3.3 Transcranial Focused Ultrasound Stimulation (TFUS)

Transcranial focused ultrasound stimulation (tFUS) uses a pressure wave of ultrasonic frequencies to induce a non-invasive yet highly localized (millimeter-level) stimulation of underlying tissue, resulting in suprathreshold neuromodulatory effects [61]. The possibility that the transcranial application of ultrasound can excite and suppress neuronal firing rates is not entirely new, demonstrated with cats in the middle of the 20th century [62]. Since that time, the influence of tFUS on neuronal activity has been investigated in several animal models, including rats, rabbits, and monkeys [63], [64].

Research using tFUS in humans is very limited, and largely constrained to measuring sensory effects in response to tFUS administration. For example, targeting the primary somatosensory cortex (S1) with tFUS can improve sensory discrimination [65], directly evoke sensory responses on the fingers and hand [66], and alter sensory evoked potentials [67]. More recent research has also demonstrated effects of tFUS targeting the primary visual cortex (V1) can produce visual phosphenes, activate brain networks (as recorded via functional magnetic resonance imaging; fMRI), and alter EEG activity [68]. tFUS can also be used at deep focal lengths suitable for targeting subcortical brain structures; in one study, researchers were able to target the thalamus and alter sensory-evoked potentials and performance on a sensory discrimination task [69].

Given the nascence of tFUS for performance enhancement, considerable barriers exist for its near-term adoption to military applications. While safety guidelines exist for diagnostic ultrasound, no formal guidelines exist for tFUS, and no systematic and rigorous studies have outlined the safety profile of tFUS for human applications. Indeed there are many parameters associated with tFUS administration that likely interact with both its safety profile and influence on neuronal activity; these include the frequency, intensity, duration, inter-stimulation interval, and pulse repetition period of tFUS administration, along with its resulting mechanical index (MI), thermal index (TI), and thermal index for cranial bone (TIC) [70]. These parameters have not been comprehensively defined or modeled in their independent and interactive effects on mechanical and thermal effects on human brain tissue, regardless of their influence on neuronal activity or behavior. For these reasons, to our knowledge tFUS has not been pursued to date in military research.

3.4 Transcutaneous Peripheral Nerve Stimulation (TPNS)

Whereas TMS, tES, and tFUS are intended to directly modulate central nervous system activity, transcutaneous (also called transdermal) peripheral nerve stimulation (tPNS) targets peripheral nervous system activity with the intent of directly and indirectly modulating peripheral and central nervous system activity, respectively [71]. Two primary forms of tPNS exist, including transcutaneous vagus nerve stimulation (tVNS) and transcutaneous trigeminal nerve stimulation (tTNS). Both techniques involve affixing two electrodes, typically near major sensory branches on the forehead or ear, and administering low-intensity (e.g., 2-4 mA) alternating (e.g., 8 Hz) current. Via vagus and trigeminal innervation of brainstem nuclei, stimulating afferent projections of these peripheral nerves may induce upstream effects on cortical brain areas relevant to cognitive function, such as the locus coeruleus (LC) and reticular formation [3], [71]–[73].

To test cognitive effects of such a mechanism, one study administered taVNS and assessed its effect on post-error slowing, a psychological phenomenon whereby participants generally slow down after committing an error [74]. Results demonstrated increased post-error slowing with taVNS relative to sham, and the authors suggested this was evidence for taVNS modulating a cognitive process thought to be dependent on NE release. Since the post-error study, additional studies have complemented that work by demonstrating positive effects of taVNS on face-name associative memory in older adults [75], conditioned fear extinction latencies [76], divergent creative thinking [77], and multi-tasking and inhibitory control [78]. There is also some evidence that even short successions of taVNS administration can reliably decrease heart rate at specific pulse widths (500µs) and frequencies (10-25 Hz) [72], and reduce sympathetic nervous system activity as indicated by increased heart rate variability [79].

While these neurophysiological and behavioral results are not as numerous as with tES, they provide compelling preliminary data that taVNS may offer utility in contexts when NE modulation may prove advantageous such as during reward learning [80], in mediating stress-induced cognitive performance declines [81], [82], and in many clinical disorders [83]. Not surprisingly, taVNS has been pursued for its potential in military performance enhancement, particularly by the U.S. Army Research Laboratory [72], [72]. Most of this research is relatively foundational, affording new understandings of how taVNS affects resting brain activity and cardiac physiology. Given the potentially advantageous effects of taVNS in modulating sympathetic nervous system activity, it is worth considering its potential for mitigating performance decrements seen under conditions of stress.

Transcutaneous trigeminal nerve stimulation (tTNS) has received substantially less attention than taVNS, but holds potential to alter stress responses and anxiety. The trigeminal, or fifth, cranial nerve has multiple afferent projections in the scalp and several facial and oral regions [84, p. 197]. The trigeminal nerve innervates the locus coeruleus, reticular formation, thalamus and multiple cortical regions, and can be stimulated by administering low-intensity transcutaneous alternating current to afferent nerve projections around the face or scalp. Stimulation of the trigeminal nerve has received substantial attention for treating neuropsychiatric disorders [85], [86], migraine [87], and epilepsy [88].

In the U.S., to our knowledge only one program is examining tTNS effects on nervous system function and behavior, sponsored by the Defense Advanced Research Projects Agency (DARPA) titled Targeted Neuroplasticity Training (TNT). This project is examining the effects of tTNS on NE and dopamine responses, human learning and memory, threat detection ability, and marksmanship training.

3.5 Cranial Electrotheraphy Stimulation (CES)

Cranial electrotherapy stimulation (CES) is a neuromodulation tool used for treating several clinical disorders, including insomnia, anxiety, and depression. It is administered by way of two electrodes positioned on the surface of the skin at bilateral anatomical positions, such as the temples or ear lobes. Like tPNS, CES likely induces subthreshold modulation of peripheral nerves, indirectly modulating central nervous system activity [89]. Studies examining CES effectiveness in treating these disorders are generally poorly designed or show high potential for conflict of interest; results from these studies are generally inconsistent in providing support for CES, though no studies have shown CES to exacerbate symptoms of these disorders [90], [91].

More recently, a very limited number of studies have examined CES for altering affect, physiology, and behavior in healthy, non-clinical samples. These studies suggest CES can alter subjective feelings of anxiety in response to acute stress, but there is no compelling evidence that these changes are accompanied by the expected endocrine responses, such as reduced alpha-amylase or cortisol levels during or following a stressor [92]–[96]. The physiological, neurochemical, and metabolic mechanisms underlying CES effects are currently unknown. Computational modeling suggests that electrical current administered with CES at the earlobes can reach cortical and subcortical regions at very low intensities, and studies using electroencephalography (EEG) and magnetic resonance imaging (MRI) show some effects on alpha band EEG activity, and modulation of the default mode network during CES administration [89], [97]–[102].

In our review of studies using CES in clinical and non-clinical populations, we found severe methodological concerns, including potential conflicts of interest, risk of methodological and analytic biases, issues with sham credibility, lack of blinding, and a severe heterogeneity of CES parameters selected and employed across scientists, laboratories, institutions, and studies. These limitations make it difficult to derive consistent or compelling insights from the extant literature, tempering our enthusiasm for CES and its potential to alter Warfighter brain or behavior in meaningful or reliable ways. The lack of compelling evidence also motivates well-designed and relatively high-powered experiments to assess how CES might modulate the physiological, affective, and cognitive responses to stress.

Ongoing U.S. defense sciences research is assessing whether CES provides any reliable or robust modulation of brain activity, endocrine responses, physiological activity, or behavior during simulated Warfighter-relevant cognitive tasks. Establishing reliable empirical links between CES administration and Warfighter performance is critical for supporting the use of CES during military training, operations, or recovery, ensuring that any benefits of CES outweigh the risks of adverse events and are not solely due to placebo effects. For example, the U.S. Army CCDC Soldier Center is pursuing this research in the context of the Measuring and Advancing Soldier Tactical Readiness and Effectiveness (MASTR-E) program.

4.0 NEUROFEEDBACK

Neurofeedback is a form of biofeedback involving the real-time monitoring of a neural signal, such as via EEG or fMRI, and the presentation of that signal to participants (e.g., visually, aurally) to assist them in regulating their own neural signal and behavior [103]. Through the closed-loop process of neurofeedback participants come to learn how to volitionally modulate their own neural activity and behavior, with potential applications to clinical rehabilitation [104], [105], therapy [106], and human performance [107].

Scientists have not settled on a single mechanistic explanation for neurofeedback effects, and debate remains regarding the state of the science and application. For example, some question the small sample sizes (i.e., many under $n \leq 20$) found in existing neurofeedback research, inconsistent sham and control procedures, unknowns regarding the ideal number of sessions, session duration, or inter-session timing to elicit effects, or the durability and generalizability of neurofeedback effects [103], [108]–[111]. Furthermore, some research demonstrates that neurofeedback can prove effective even with non-veridical closed-loop feedback (e.g., random signals, or another participant’s signals), suggesting that merely believing in neurofeedback and/or engaging cognitive control networks might underlie some neurofeedback effects [112], [113].

Despite the uncertainty of the science, international defense research has pursued neurofeedback for several applications including attention training and accelerating knowledge acquisition. For example, in the U.S., DARPA and the Army Research Office (ARO) and Army Research Laboratory (ARL) have funded neurofeedback research examining whether EEG-generated neurofeedback regarding arousal states can influence physiological signals (pupil diameter and heart rate variability) and alter performance on a stressful boundary-avoidance task [114]. The authors found evidence for reduced arousal responses in the veridical (versus sham) neurofeedback condition, and higher performance in the boundary-avoidance task. ARO and ARL have also funded research attempting to develop more comprehensive mechanistic models of neurofeedback on the brain and behavior [115]. The Air Force Research Laboratory has funded research using fMRI neurofeedback for the training of working memory capacity, demonstrating significantly higher improvements on an n-back task relative to a control group [116], [117].

5.0 METHODOLOGICAL CHALLENGES FOR NEUROENHANCEMENT

As with any nascent scientific discipline, several methodological and conceptual challenges exist that make it difficult to envision near-term application to military training or operations. This section details some of these challenges.

5.1 Side Effects and Adverse Events

Experimental and meta-analytic research have demonstrated varied side effects and adverse events associated with different neuroenhancement techniques. Transcranial and transcutaneous electrical stimulation commonly induces the cutaneous perception of tingling, itching, burning, pain, and fatigue. Most participants experience at least one symptom of skin irritation with tES [118], with substantially fewer participants experiencing them with taVNS [119]. Adverse effects of tES tend to be short-lived and mild to moderate in subjective intensity [45], [120]–[122].

With TMS, risks include seizure induction, hypomania , headache or local pain, hearing changes, burns from electrodes, or excessive brain tissue heating [123]. The risk of seizure induction with high frequency rTMS is estimated at lower than 1% in non-epileptic samples, hypomania is rare but possible with left prefrontal high frequency rTMS, transient headache or neck pain are frequent with rTMS [124] and the other risks are negligible or otherwise unreported [123].

With tFUS, a review of participant (N = 64 across 7 experiments) reports of side effects experienced following tFUS administration demonstrated no serious adverse effects, but an approximately 11% rate of mild to moderate side effects [125]. These included sleepiness, anxiety, muscle twitches, attention challenges, and neck pain, similar to some side effects seen with tES or TMS. Another review demonstrated that brain microhaemorrhages can occur when stimulation intensities exceed safety criteria, as can unintentional opening of the blood-brain barrier, and neuronal damage or death [70].

With CES, the most frequently reported side effects are vertigo, skin irritation, and headaches [126], which are estimated to occur about 1% of the time [127]. In user manuals and reports published by device manufacturers, the guidance is to reduce stimulation intensity to mitigate any reported side effects; of course, in a research setting this strategy leads to differences in stimulation intensity across participants. In studies not conducted or published by authors associated with a CES device manufacturer, frequency of side effects is mixed. In one study, 25% (3/12) participants self-withdrew due to discomfort with side effects of dizziness or headache. In two other studies, there were no significant differences in reported side effects between active and sham CES groups [128], [129].

With any device using magnetic or electrical fields to alter neuronal activity, there is also a risk that long-term, repeated use of these devices may permanently alter brain morphology or functional connectivity in unknown ways. Long-term epidemiology studies may prove valuable in elucidating these risks, especially as devices continue to increase in consumer availability and home and occupational use.

5.2 Risk of Bias

The Cochrane Risk of Bias (RoB 2) tool provides a mechanism for formalizing risk of bias that may be present in randomized trials [130]. Five key domains are included when assessing risk of bias, including bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

The randomization process involves the allocation of participants into intervention groups randomly and in an adequately concealed manner, and assesses and controls for baseline differences between intervention groups. For example, in a study examining the effects of rTMS over the primary motor cortex on motor sequence learning, participants were assigned to intervention groups without reported random assignment [131]. Similar reporting deficiencies were found when examining studies using tDCS, taVNS, and CES [19], [79], [132].

Deviations from intended interventions involves participants and/or researchers not adequately blinding assigned interventions. Most tDCS studies are single- rather than double-blinded, increasing the likelihood that the intervention was not adequately concealed from participants [19]. Even with participant blinding, differences in skin irritation between active and sham tDCS conditions can cause participants to become aware of their assigned intervention [133]. This is not unique to tDCS; designing adequate sham procedures to effectively blind participants is challenging for any neuromodulatory technique. For example, active tFUS can elicit visual phosphenes which are absent in sham conditions [68], and sham TMS procedures can induce sensory and motor side effects that can selectively and reliably alter task performance [134].

Missing outcome data involves a report not covering all participants, manipulations, measures, and outcome data. A review of neuroenhancement studies using terms such as “published elsewhere,” “reported separately,” “participants were excluded,” “part of a larger study,” and “data were excluded” was conducted to assess the frequency of participant and/or data omission in published works. Thousands of studies were identified across the tES, TMS, taVNS, tTNS, CES, and Neurofeedback domains. Critically, many of these instances either did not adequately justify omission of participants, measures, or data, or missing aspects were ultimately not published elsewhere (to date). Examples include reporting behavioral and neuroscientific outcomes of tES in separate publications with different exclusion criteria [135], reporting subjective and objective measures of neurofeedback effects in separate publications [136], and excluding participants from analysis without ample statistical justification [137].

Measurement of the outcome assesses whether the chosen method for measuring outcomes was appropriate and consistent across intervention conditions. For example, one criticism of neurofeedback research is the extent to which outcome measures adequately reflect transfer of knowledge or skills [103], [138], [139]. Indeed, selecting appropriate measures of near-, medium-, and far-transfer through formal taxonomy is important but also very challenging [140], [141].

Selection of the reported result assesses whether analysis and reporting of outcomes are comprehensive and followed an a priori plan and are not “cherry-picked” from the outcomes of multiple analyses. It is unfortunately not uncommon to see neuroenhancement publications selectively reporting response times or accuracy on a task, while omitting analysis of the other measure [142]. One method for encouraging reporting in accordance with a pre-specified plan is registered reports, which involve submission of a manuscript detailing all hypotheses and analyses prior to data collection [143]. Neuroenhancement research would benefit from this mechanism that helps reduces the inherent disincentivizing of null or unexpected results.

5.3 Reproducibility

Scientists have considered the disproportionately positive results published in the psychological sciences, leading to what some have considered a “replication crisis” [144]. In its most extreme form, scientists have argued that current institutional incentives for publishing positive results leads to an estimate that “most current published research findings are false” [145]. At the other extreme, some scientists have argued that replication attempts are a waste of time and stifle creativity (and perhaps result from stifled creativity) [146], [147]. Between these two is a more progressive perspective that suggests that even apparent failures to replicate might be informative for advancing experimental methods and theory [146].

One theory of how science progresses is through phases of initial enthusiasm about exciting and innovative methods and results, the proposal of several mechanistic and conceptual models and theories, an accumulation of overall ambiguous results surrounding a methodology, and then a slow loss of interest in a phenomenon and its associated theories [148]. In the long run, many of these theories are disregarded rather than formally falsified, and there is a trend (called the decline effect) for the strength of a phenomenon to diminish over time with subsequent study or replication attempts [149].

Neuroenhancement research is not immune to the replication crisis, and scientists and practitioners must use caution when interpreting strong claims about innovative techniques derived from low-power or possibly biased research. In the neurofeedback domain, research has been criticized for having insufficient methodological detail to support replication attempts [150], excessively small sample sizes [151], and limited reproducibility [152]. Similar criticisms have arisen in the context of tES [11], [31], [32], TMS [153]–[155], CES [132], [133], and transcutaneous peripheral nerve stimulation [76], [156]. It is likely that newer neuroenhancement techniques, such as tFUS, will encounter such criticisms as more replication attempts and original research are conducted.

There are a few things that neuroenhancement research can do to improve the reproducibility of research. First, scientists and publishers should promote and enforce sample sizes that maximize power and minimize the likelihood of a Type I error. Small sample sizes and low statistical power undermine our ability to identify true effects: it is well-established that low power studies are unlikely to find a true effect, hold low predictive value when an effect is found, and the magnitude of any identified effects is likely inflated [157, p. 201]. Second, scientists, institutions, and publishers should assign equal value to manuscripts reporting null or counter-intuitive results, assuming sample size criteria are met [158], [159]. A publication bias towards positive findings occurs not only in original science, but also in replication attempts, and contaminates theory development and the systematic aggregation of results via meta-analysis [160]. Third, registered reports and open access data sharing are an effective tool for reducing publication bias and increasing the transparency and reproducibility of science [159, p. 20].

5.4 Parameter Heterogeneity

Each neuroenhancement technique has myriad parameters that are often selected and manipulated inconsistently or without ample justification; instead, in many cases neuromodulatory parameters are selected due to familiarity or convenience. Furthermore, few computational models exist that attempt to characterize and predict the effects of independent and interactive parameter manipulation on human performance outcomes.

With TMS and rTMS, parameters include the number and duration of trains (the successive repetitions of stimulation within a block), the intertrain interval, stimulation site and intensity, and the number of applied pulses [161, p.]. With tES, parameters include the number and type of electrodes, the stimulation sites, and the timing, intensity, frequency, and duration of stimulation [19], [30], [121]. Similarly complex parameter spaces exist for all other neuroenhancement techniques identified in this report.

The result is a highly heterogeneous literature that not only limits reproducibility but also makes it challenging to optimize the parameter space to facilitate reliable and robust performance outcomes. Meta-regression modeling efforts by the United States Army are aimed at better characterizing and optimizing this parameter space for tES, affording a more targeted selection of parameters to suit contexts and tasks and increase the likelihood of realizing positive effects on human performance.

5.5 Conflicts of Interest

When professional judgments or activities, such as selecting experimental conditions or which data to analyze and report, are affected by a secondary interest such as financial gain, conflicts of interest (COI) can occur [162]. For example, when research is sponsored by the manufacturer or retailer of a neuroenhancement technology, this can interfere with a primary interest to conduct research in an honest, methodical, or sound manner. Furthermore, COIs can occur when a scientist or practitioner partners with or is otherwise involved in establishing, sustaining, or managing any entity that benefits from the outcome of the research.

The proliferation of consumer-grade neuroenhancement technologies has made COI a considerable risk for the integrity of reported science. For example, in our review of the CES literature we found that at least half of the reported CES research was either funded by a CES manufacturer, or authored by the founders, owners, management, or board members of CES manufacturers or retailers [126], [127], [163]–[166]. Of course, these authors stand to benefit from positive research outcomes, increasing the likelihood that study results are influenced (intentionally or unintentionally) by potential COI.

6.0 ADDITIONAL CHALLENGES FOR NEUROENHANCEMENT

The group identified several additional important considerations for the development and application of cognitive neuroenhancement techniques in military settings. This section summarizes these considerations.

6.1 Ethical Considerations

Neuroenhancement research and technological developments have inspired many scientists, practitioners, and philosophers to question the ethical foundations of altering brain structure or function, thought processes, and behavior [167]. One way to think about the ethical implications of neuroenhancement is, in addition to safety, to focus on the following principles: beneficence, autonomy, and justice [168].

Beneficence involves actions with the goal of benefitting the good of other persons, such as through kindness or generosity. In research, beneficence is associated with maximizing benefits and minimizing risks, and doing no harm, and is a cornerstone of research protocol reviews [169]. Calculating cost-benefit analyses associated with neuroenhancement techniques can be difficult when long-term effects of any given technique are relatively unknown. Just as with stimulant administration having long-term risks of addiction and misuse, neuromodulatory techniques may carry long-term negative consequences for well-being, which may be bolstered by the availability of commercial devices and lack of FDA oversight.

Autonomy involves respecting and avoiding undue influence on each person’s ability and right to self-govern. Military personnel present a unique case for autonomy, given that choosing to serve involves limiting some self-governance [167]. This situation increases the likelihood of coercion and exposes military personnel to undue safety risks. While in some cases neuroenhancement might be expected to reduce risk of injury or death [170], in other cases the outcomes might be unknown. Indeed, any intervention designed to exogenously alter brain activity, thought, character, and behavior is also possibly decreasing the individual’s ability to self-govern. This possibility is not unique to military populations, but the risk may be amplified given a desire to conform and excel.

Justice, specifically distributive justice, dictates that inequities in access and availability with neuroenhancement techniques should be minimized [167]. In other words, if performance can indeed be reliably and robustly enhanced, who should have access to such capabilities? One can easily imagine the situation where only those who can afford consumer neuroenhancement technologies will benefit from their effects on performance, widening disparities and reducing distributive justice. On the other hand, some believe that increasing consumer access to neuroenhancement will ultimately better society overall as all levels of the socio-economic status eventually reap the benefits [171, p. 200].

In addition to beneficence, autonomy, and justice, there are several additional ethical considerations. These include the legal implications associated with reduced self-governance under the influence of neuroenhancement techniques [167], [172], distinctions between excellence in process versus outcome [173], and potential threats to society’s notions of personhood. There is also a gap in regulatory oversight of neuroenhancement techniques, particularly relative to other stimulants and pharmaceuticals intended to enhance performance [174, p. 20], demonstrating the relevance and need for comprehensive frameworks to understand and model the ethics of neuroenhancement and inform regulation in this domain.

Policies and procedures for the selection and deployment of neuroenhancement techniques in military contexts are sorely needed to support safety and beneficence, and protect individual autonomy.

6.2 Net Zero-Sum Gains

Many theoretical models attempt to capture the mechanisms that may explain and predict neuroenhancement effects on cognitive performance. In the transcranial electrical stimulation domain, these include theories of balance effects, sliding scale, input specificity, stochastic resonance, activity-selectivity, and enhancement through entrainment of oscillatory patterns [11], [38]. Many modern theories rely on sliding scale models, which postulate that anodal stimulation increases neuronal excitability (depolarization), and cathodal stimulation does the opposite (hyperpolarization).

One sliding scale model, the zero-sum model, suggests that stimulation causes a net zero-sum gain through antagonistic modulation of various brain regions [11]. The idea is that the finite metabolic resources and inherent interdependence of brain regions will produce a situation where activations in one area may be entirely compensated for by deactivations in another area; in other words, any gains experienced through neuroenhancement may involve the redirection of shared energetic resources towards the upregulated region or network. Reviews on this topic suggest that up to nearly half of results using non-invasive brain stimulation may be explained by the zero-sum model [5], [175]. If so, many existing studies examining the effects of neuroenhancement approaches within a single domain such as working memory, emotion regulation, or motor output, may be overestimating the extent to which any enhancement can be achieved in more realistic contexts that demand more diverse central processing.

Indeed, military operations involve the interaction between numerous perceptual, cognitive, and emotional processes over time to enable sustained and accurate performance. It could be the case that any identified advantages, for example in inhibitory control, may be accompanied by yet unknown negative effects in a different domain. For example, upregulation of the fronto-parietal control network [176], [177] via tES targeting the dlPFC could induce a redirection of metabolic resources away from other brain networks, such as the salience network [178]. In this manner, neuroenhanced performance may indeed induce enhanced processes reliant upon executive control, such as flexibly shifting between task sets, or inhibiting prepotent responses; however, this enhancement may be accompanied by a decreased ability to detect and attend to salient, goal-relevant events. Such trade-offs could prove detrimental to operational performance in military contexts: while this type of neuroenhancement might improve, for example, the ability to flexibly switch between radio communications and attending to interactions with a crowd of civilians, it could theoretically result in concurrent increased latencies to detect important changes in the environment (e.g., appearance of a weapon). At this point, it is unknown how any net zero-sum effects will be realized at the macro-level (e.g., neural networks) or micro-level (e.g., intracellular mechanisms), whether any neural costs will prove costly for behavior, how long any such costs might last, and whether they are reversible in all situations.

Continuing research at the intersection of cognitive and defense sciences must consider these parameters when calculating cost-benefit analyses; to do so, such calculations must be informed by empirical research outcomes. This points to the benefit of research aimed at understanding not only the effect of a neuroenhancement strategy on a targeted process of interest, but also on processes that may not be of direct interest but possibly important to real-world functioning and eventual military application.

6.3 Undefined Biological Limits of Human Performance

The concept of human enhancement has engendered some controversy in the literature related to its measurement and promotion. The group discussed one specific controversy, namely that if neuroenhancement aims to enhance human capacity beyond previously achievable levels, then we must reliably quantify previously achievable levels. Without establishing this important performance baseline there is no meaningful way of ascertaining whether enhancement has occurred as a function of any neuroenhancement intervention. There are two primary ways of conceptualizing performance enhancement. First is simple improvement of performance relative to a non-enhanced state; for example, administering active tDCS to the prefrontal cortex may accelerate working memory capacity training relative to sham. Some might consider this a form of performanceenhancement, improving a metric such as accuracy, response times, and/or sensitivity over time relative to a control condition.

A second way to conceptualize performance enhancement is improvement relative to human biological norms. In this case, performance enhancement would necessitate exceeding biological norms [179, p. 201]. Biological norms can be assessed at the population level by defining theoretical limits to human performance, at the group level by understanding peak team performance, and at the individual level. We argue that peak performance has not been adequately defined at any of these levels of analysis.

Let us consider the case of simple reaction times. In a simple reaction time task, a stimulus is presented in one or more sensory modalities, and a participant is tasked with responding as quickly as possible to the onset of the stimulus [180]. For example, a visual stimulus (a dot) might be presented on a computer monitor at pseudo-random intervals, and the participant might respond as quickly as possible to its presentation by pressing the spacebar on a keyboard.

What is the biological limit of human simple reaction time? For the current example, let us disregard issues with timing and latency inherent to computer hardware and software, the effects of stimulus onset asynchrony (SOA), the potential influence of incentives, motivation, attention, preparatory motor responses, and practice [181], [182], and any other experimental parameters. Instead, let us solely consider the human biological system, which provides a few ways of approaching the question of biological limits to reaction time.

One method is by considering models of the human visual and motor systems, and the lowest latency with which a human could theoretically sense and react to a visual stimulus. In these models, a visual sensation would begin with light hitting the retina and activating photoreceptors, triggering a cascade of neural activity through the lateral geniculate nucleus of the thalamus, and to the primary visual cortex. Information would then be carried through higher levels of the visual cortex and through dorsal stream pathways to parietal and frontal regions of the cortex. From retina to primary visual cortex, magnetoencephalography (MEG) studies have demonstrated neural latencies averaging 71 milliseconds [183]. Further along, indirect inhibitory connections between the primary visual cortex and primary motor cortex are relatively low-latency and thought to be on the order of approximately 15-20 milliseconds [184]. Thus, theoretically it should take less than 100 milliseconds for visual information to be sensed and information to propagate to the primary motor cortex and potentially play a role in an efferent motor command. Studies using MEG and limb electromyography (EMG) recordings demonstrate that it takes approximately 160 milliseconds from a visual stimulus onset to an EMG onset (e.g., an arm movement), suggesting that the motor command takes approximately 60 milliseconds to initiate [185]. That same study shows that it takes another 70 milliseconds for movement to occur after the onset of EMG activity. Together these findings suggest that the human visuomotor system takes approximately 230 milliseconds, on average, to sense, interpret, and motorically respond to visual input (i.e., to traverse the phases of stimulus coding, stimulus-stimulus translation, stimulus-response translation, and response selection [186]). Classic reviews of simple reaction times find similar results, averaging about 220 milliseconds [187, p. 1]. Of course, the estimate of 220-230 milliseconds for a visual reaction time is simply the mean of a larger distribution with left and right tails; the left tail is particularly interesting as it potentially speaks to the biological limits of speeded reaction time.

Unfortunately, most reported simple reaction time data is subjected to outlier removal, which typically removes data falling below and/or above criterion values; for example, exploring the extant literature, one example study used a response window of 110-1000 milliseconds, removing any reaction times falling below (considered premature) or above (considered delayed) these criteria [188]. Others have used windows of 100-1000 [189], [190], 100-500 [191], or only a lower limit of 150 ms [192]. Selecting variable thresholds for data exclusion introduces uncertainty in attempting to define the distribution surrounding a theoretical minimum latency for reaction times.

A second major challenge is reliably dissociating premature versus valid responses at the lower end of any response window. For example, if a participant responds in 110 milliseconds to a visual stimulus onset, should that response be considered valid or premature (i.e., a false alarm)? What if the response occurs 99 milliseconds after visual stimulus onset? We did encounter one study that attempted to define categorical boundaries of reaction times corresponding to very good, good, normal, not bad, or bad latencies [193]. At the peak of performance on a simple reaction time task, the authors suggested that reaction times would fall below 190 ms. However, this suggestion was derived from a study of only 10 college athletes performing a total of about 20 minutes of testing.

An alternative technique is to attempt measuring optimal performance of an individual or group, and then asking whether neuroenhancement reliably causes deviation from that baseline. For example, scientists could measure an individual's response time in myriad circumstances, at varied times of day, temperatures, hydration and nutritional status, stimulant consumption levels, motivational states, and sleep status. Only by identifying the optimal combination of contextual variables will the scientist be able to measure the individual's true peak performance. Of course, one would need sufficient samples at peak performance to characterize the nature of that distribution and afford statistical comparison to performance during a neuroenhanced state. Enhancement, in this case, would only occur when a neuroenhancement method causes individual peak performance to significantly (in a statistical sense) exceed identified peak performance.

Even within the domain of simple reaction time, identified peak performance baselines will likely be considerably different across sensory modalities. For example, the auditory system is generally faster than the visual system, and the tactile system is generally faster than the auditory system [191], [194]. Multisensory inputs are even faster than single modalities, a phenomenon referred to as redundancy gain [195]. Thus, even for the seemingly most basic of human behaviors, simple reaction time, there is considerable complexity in adequately defining peak performance. The situation likely only becomes more complex when considering tasks involving relatively high central processing demands. For example, response inhibition and problem-solving tasks are particularly heterogeneous in parameters, elicit highly variable performance, and are impacted by many endogenous and exogenous factors.

7.0 FUTURE DIRECTIONS FOR NEUROENHANCEMENT

The group identified several additional important considerations for the development and application of cognitive neuroenhancement techniques in military settings. This section summarizes these considerations.

7.1 Improved Mechanistic Models and Software Tools

Existing mechanistic models of neuroenhancement, including non-invasive brain stimulation and neurofeedback, are very limited. For example, a cursory literature review indicated that over the past year alone, hundreds of published papers refer to anodal tES as excitatory, and cathodal as inhibitory. This simple and intuitive dichotomy between anodal and cathodal stimulation eschews the inherently complex interactions between neurons, electric field potentials, neural circuits, and behavioral outcomes [196], [197], and has been repeatedly falsified through modeling and empirical work. For example, neuronal orientation relative to an induced electric field can differentially produce depolarization versus hyperpolarization of neuronal membranes [198], [199]. The same challenges arise when considering polarity influences on neurons with varied morphology and function [200]. The fact that scientists continue to rely on such outdated mechanistic models points to a need for newer and more broadly disseminated models that attempt to leverage the apparently intuitive aspects of sliding scale models.

The possibility that brain stimulation, including at least TMS [201] and tES [200], can induce non-linear effects on brain and behavior, introduces challenges for existing mechanistic models. Of course, it also introduces challenges for identifying potential stimulation intensities and durations for real-world application, particularly if different individuals show varied non-linear effects of stimulation [202]. Non-linear models, such as the ones using neural network attractor models [200], carry potential for helping to define and optimize stimulation protocols to individuals, contexts, and tasks. To the extent that such models are biologically plausible, they can guide validation efforts with optimized stimulation protocols in laboratory and field contexts, helping to bridge the gap between model-based simulation and real-world behavior.

Once more robust and validated mechanistic models of neuroenhancement effects on brain and behavior are developed, there is an opportunity to develop software tools to guide the use of neuroenhancement tools in military contexts. Such tools could be used by end users, trainers, and commanders seeking to enhance the competitive edge of military units. Existing software tools distributed with research- and consumer-grade tES devices typically provide basic parameter manipulation; for example, the consumer-grade Foc.us v3 device allows users to select various tES waveforms (tDCS, tACS, tRNS), intensities (0.1 to 2.0mA), and stimulation durations (up to 40 minutes). Research-grade devices, such as those from Neuroelectrics (Barcelona, Spain) and Soterix Medical (New York, NY), provide highly flexible parameter manipulation, and accompanying software can predict and optimize electrical current propagation for specific montages and cortical and subcortical targets. However, no guidance is provided to customize parameters as a function of the individual, context, or task. Current mechanistic models of tES effects on brain and behavior do not afford any such customization, but given evidence that subtle alterations in parameters such as intensity and duration can alter, if not reverse, tES effects, advancing models and transitioning them to intuitive software tools is essential for successful application to military training and operations.

7.2 Addition by Subtraction and Subtraction by Addition

One emerging but under-researched theory of how neuroenhancement may induce effects is through addition-by-subtraction [5]. This theory emphasizes research demonstrating that reducing activity in brain regions that compete with a process of interest can lead to performance gains. This method is of neuroenhancement contrasts the typical targeting of brain regions ostensibly involved in supporting task performance, instead targeting other regions that may be disruptive to task performance. There is some compelling evidence for addition-by-subtraction effects occurring in the TMS literature. For example, in a visual search study, TMS targeting a motion processing region of the occipital cortex produced increased or decreased response times as a function of whether task required processing or not processing motion-based information, respectively [13]. When the task only involved processing form and color information, inhibiting the motion processing regions enhanced task performance, suggesting that they were interfering with parallel processes occurring in adjacent regions of the occipital cortex. Similar addition-by-subtraction effects were found in an object discrimination task with TMS targeting the temporal cortex [203], studies examining the reduction of cross-hemispheric inhibition [204], [205], and a study showing reduced costs of incongruent Stroop trials with rTMS targeting the anterior cingulate cortex (ACC) [206]. A more complete tabulation of TMS studies suggesting feasibility of an addition-by-subtraction mechanism can be found in the original theoretical position paper [5].

We propose that similar results may be found with tES. For example, downregulating inhibitory regions or conversely upregulating facilitatory regions that are functionally connected with task-critical regions, could prove advantageous to task performance. If so, this would open the door to new methodologies that indirectly target functionally connected regions with the intent of altering activity in distant regions. Such a methodology could prove advantageous, for instance, by using a superficial neuroenhancement method such as tDCS or tACS to indirectly modulate functionally-connected subcortical regions [52], [207].

From a scientific perspective, as we continue to research neuroenhancement in academic and the defense science community, we have come to understand that brain stimulation may be just as likely to do nothing or negatively influence performance as it is to enhance performance.

In contrast to addition by subtraction, the concept of subtraction by addition pertains the possibility that neuroenhancement tools can be used to negatively influence performance. We term this a neurodiminishing effect, and envision that such a strategy could be used in the future by adversarial forces. Indeed the very same technologies that are intended to enhance performance on a set of processes and tasks, may be used to diminish performance by selectively tweaking various parameters (such as stimulation polarity, intensity, frequency, location, duration). In other words, the devices that are intended to make Warfighters smarter, faster, and stronger, can be modified to produce neurodiminishment – maybe lower intelligence, slow down reactions, or weaken the body.

In some scenarios, neurodiminishment might be advantageous from a military perspective. For example, one might find that impairing executive function can improve the effectiveness of interrogation, that impairing memory consolidation can reduce the likelihood of developing a stress disorder, or shutting down rumination under stress can improve sleep quality. We can also imagine how neurodiminishment can be used in the opposite manner by adversaries to directly exert power and influence over our Soldiers. There are two primary things to think about here.

First, neuroenhancement technologies will likely become a target for electronic warfare, at a minimum rendering them temporarily ineffective, or at an extreme causing them to administer frequencies or intensities that effectively degrade performance. In other words, electronic warfare may be able to exert its influence directly upon the nervous system of individual Warfighters.

Second, we are currently at the point in neuroenhancement technology that devices are becoming increasingly portable, untethered, and remotely controlled. While current technologies require Warfighters to wear devices on or about their heads, future technologies will very likely be able to induce neurodiminishing effects using stand-off directed energy sources. At a gross level, such stand-off neurodiminishing technologies could temporarily immobilize Soldiers, and at a more refined level, such approaches could selectively alter brain activity and behavior in undesirable ways and alter the strategic advantage.

Given that many neuroenhancement technologies can be used in ways that are imperceptible to the user (in other words, they may not hear, see, or feel it working), neurodiminishing effects could be administered without the awareness of the agent. In this manner, neuroenhancement technologies may be used against military forces in future warfare, potentially causing them to become less intelligent, slower, or weaker, but now at range, and possibly unbeknownst to them.

7.3 Closed-loop Neuroenhancement

By combining neural sensing, machine learning, and neurostimulation modalities, closed-loop neuroenhancement devices are designed to dynamically modulate stimulation parameters as a function of sensed and inferred mental and/or physical states. In contrast to neurofeedback, closed-loop neuroenhancement does not involve conveying information about mental or physical states to the user. In the motor rehabilitation domain, closed-loop neurostimulation systems have resulted in tremendous gains for patients suffering from diverse mental or physical impairments due to stroke, injury, epilepsy, Parkinson’s disease, and other disorders [208], [209]. Through real-time sensing and adaptive neurostimulation, typically via implanted stimulation devices, physicians can exert unprecedented control over the symptoms of these disorders.

Closed-loop neuroenhancement techniques have also begun to receive attention in the domain of human performance enhancement. In the sleep domain, researchers have developed closed-loop sleep optimization systems that measure sleep spindles and phases and adaptively trigger tACS to augment endogenous slow-wave oscillations [210], [211]. The idea is that by enhancing slow-wave oscillatory activity, users can achieve improved sleep (onset latency, quality, duration) and reap more of the sleep-related advantages seen in recovery trajectories and memory consolidation [212]. This is one exciting avenue for closed-loop neuroenhancement, being pursued by the U.S. Army Walter Reed Army Institute of Research’s (WRAIR) Sleep Research Center, which is working to validate the effects of closed-loop tACS on the quality of sleep achieved during overnight rest and tactical napping; they are also working with a device manufacturer to prototype portable closed-loop neurostimulation devices to enhance sleep in military operational contexts.

Closed-loop neuroenhancement may also prove valuable for acutely enhancing task performance in other military contexts and tasks, such as counteracting fatigue and drowsiness effects in prolonged vigilance tasks [213], mitigating sleep deprivation effects on diverse mental functions , preventing acute stress-related effects on performance and memory, or dynamically altering motivational states to suit task demands . Of course, closed-loop neuroenhancement relies upon success in solving several research and development challenges. First, it requires sensitive and specific sensing and inference of brain and mental states that are relevant and causally-linked to successful task performance [214], [215]. Change point estimation is a challenging modeling problem, especially when considering brain dynamics that will likely have very low signal to noise ratios in real-world environments [216]. Second, closed-loop neuroenhancement requires high fidelity targeting of brain regions that are reliably linked to modulating relevant task outcomes [217].

Given the inherent challenges related to identifying suitable parameters that are individualized and catered to the context and task, accomplishing this goal will likely necessitate several decades of continuing research. Finally, given evidence that even short bouts of neurostimulation can produce long-lasting effects on brain and behavior [218]–[221], and that repetitive neurostimulation can sometimes produce paradoxical effects [222], the potential influences of repeatedly and briefly triggering stimulation need to be better elucidated.

8.0 CONCLUSIONS

Non-invasive brain stimulation (NIBS) carries potential to help warfighters accelerate training and knowledge acquisition, and sustain, optimize, and enhance task performance. Enthusiasm for this potential, however, is tempered by several theoretical, ethical, mechanistic, and practical limitations that slow the eventual adoption of NIBS in military contexts. These are not insurmountable challenges, though they do slow scientific progress and increase the uncertainty of research outcomes. We presented several directions for continuing research that can help push the boundaries of science and application, increase scientific and technical knowledge, and elucidate near- and far-term applications of NIBS to military settings.

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REFERENCES

[1] V. P. Clark and R. Parasuraman, “Neuroenhancement: Enhancing brain and mind in health and in disease,” *NeuroImage*, vol. 85, pp. 889–894, Jan. 2014, doi: 10.1016/j.neuroimage.2013.08.071.

[2] M. J. Farah, “The unknowns of cognitive enhancement,” *Science*, vol. 350, no. 6259, pp. 379–380, Oct. 2015, doi: 10.1126/science.aad5893.
[3] T. T. Brunyé *et al.*, “A Review of US Army Research Contributing to Cognitive Enhancement in Military Contexts,” *J Cogn Enhanc*, Feb. 2020, doi: 10.1007/s41465-020-00167-3.
[4] W. Klomjai, R. Katz, and A. Lackmy-Vallée, “Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS),” *Annals of Physical and Rehabilitation Medicine*, vol. 58, no. 4, pp. 208–213, Sep. 2015, doi: 10.1016/j.rehab.2015.05.005.
[5] B. Luber and S. H. Lisanby, “Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS),” *NeuroImage*, vol. 85, pp. 961–970, Jan. 2014, doi: 10.1016/j.neuroimage.2013.06.007.
[6] B. Dräger, C. Breitenstein, U. Helmke, S. Kamping, and S. Knecht, “Specific and nonspecific effects of transcranial magnetic stimulation on picture-word verification,” *Eur. J. Neurosci.*, vol. 20, no. 6, pp. 1681–1687, Sep. 2004, doi: 10.1111/j.1460-9568.2004.03623.x.
[7] L. A. Boyd and M. A. Linsdell, “Excitatory repetitive transcranial magnetic stimulation to left dorsal premotor cortex enhances motor consolidation of new skills,” *BMC Neurosci*, vol. 10, no. 1, p. 72, Jul. 2009, doi: 10.1186/1471-2202-10-72.
[8] K. Yamanaka, B. Yamagata, H. Tomioka, S. Kawasaki, and M. Mimura, “Transcranial magnetic stimulation of the parietal cortex facilitates spatial working memory: near-infrared spectroscopy

study," *Cereb. Cortex*, vol. 20, no. 5, pp. 1037–1045, May 2010, doi: 10.1093/cercor/bhp163.

[9] B. D. Earp, A. Sandberg, G. Kahane, and J. Savulescu, "When is diminishment a form of enhancement? Rethinking the enhancement debate in biomedical ethics," *Front Syst Neurosci*, vol. 8, p. 12, 2014, doi: 10.3389/fnsys.2014.00012.

[10] I. M. Harris, C. T. Benito, M. Ruzzoli, and C. Miniussi, "Effects of right parietal transcranial magnetic stimulation on object identification and orientation judgments," *J Cogn Neurosci*, vol. 20, no. 5, pp. 916–926, May 2008, doi: 10.1162/jocn.2008.20513.

[11] A.-K. Brem, P. J. Fried, J. C. Horvath, E. M. Robertson, and A. Pascual-Leone, "Is neuroenhancement by noninvasive brain stimulation a net zero-sum proposition?," *NeuroImage*, vol. 85, pp. 1058–1068, Jan. 2014, doi: 10.1016/j.neuroimage.2013.07.038.

[12] M. Oliveri, L. Zhaoping, G. R. Mangano, P. Turriziani, D. Smirni, and L. Cipolotti, "Facilitation of bottom-up feature detection following rTMS-interference of the right parietal cortex," *Neuropsychologia*, vol. 48, no. 4, pp. 1003–1010, Mar. 2010, doi: 10.1016/j.neuropsychologia.2009.11.024.

[13] V. Walsh, A. Ellison, L. Battelli, and A. Cowey, "Task-specific impairments and enhancements induced by magnetic stimulation of human visual area V5.," *Proc Biol Sci*, vol. 265, no. 1395, pp. 537–543, Mar. 1998.

[14] M. Kobayashi, "Effect of slow repetitive TMS of the motor cortex on ipsilateral sequential simple finger movements and motor skill learning," *Restorative Neurology and Neuroscience*, vol. 28, no. 4, pp. 437–448, Jan. 2010, doi: 10.3233/RNN-2010-0562.

[15] M. Kobayashi, S. Hutchinson, H. Théoret, G. Schlaug, and A. Pascual-Leone, "Repetitive TMS of the motor cortex improves ipsilateral sequential simple finger movements," *Neurology*, vol. 62, no. 1, pp. 91–98, Jan. 2004, doi: 10.1212/wnl.62.1.91.

[16] M. Kobayashi, H. Théoret, and A. Pascual-Leone, "Suppression of ipsilateral motor cortex facilitates motor skill learning," *European Journal of Neuroscience*, vol. 29, no. 4, pp. 833–836, 2009, doi: 10.1111/j.1460-9568.2009.06628.x.

[17] D. L. Gilbert, M. A. Garvey, A. S. Bansal, T. Lipps, J. Zhang, and E. M. Wassermann, "Should transcranial magnetic stimulation research in children be considered minimal risk?," *Clinical Neurophysiology*, vol. 115, no. 8, pp. 1730–1739, Aug. 2004, doi: 10.1016/j.clinph.2003.10.037.

[18] A. Antal and W. Paulus, "Transcranial alternating current stimulation (tACS)," *Front. Hum. Neurosci.*, vol. 7, 2013, doi: 10.3389/fnhum.2013.00317.

[19] J. Dedoncker, A. R. Brunoni, C. Baeken, and M.-A. Vanderhasselt, "A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) Over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: Influence of stimulation parameters," *Brain Stimulation*, vol. 9, no. 4, pp. 1–17, 2016, doi: 10.1016/j.brs.2016.04.006.

[20] W. Paulus, "Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods," *Neuropsychological Rehabilitation*, vol. 21, no. 5, pp. 602–617, Oct. 2011, doi: 10.1080/09602011.2011.557292.

[21] G. B. Saturnino, A. Antunes, and A. Thielscher, "On the importance of electrode parameters for shaping electric field patterns generated by tDCS," *NeuroImage*, vol. 120, pp. 25–35, Oct. 2015, doi: 10.1016/j.neuroimage.2015.06.067.

[22] A. J. Woods *et al.*, "A technical guide to tDCS, and related non-invasive brain stimulation tools," *Clinical Neurophysiology*, vol. 127, no. 2, pp. 1031–1048, 2016.

[23] R. C. Kadosh, "Using transcranial electrical stimulation to enhance cognitive functions in the typical and atypical brain," *Translational Neuroscience*, vol. 4, no. 1, pp. 20–33, Mar. 2013, doi: 10.2478/s13380-013-0104-7.

[24] E. Santarnecchi, A. K. Brem, E. Levenbaum, T. Thompson, R. C. Kadosh, and A. Pascual-Leone, "Enhancing cognition using transcranial electrical stimulation," *Current Opinion in Behavioral Sciences*, vol. 4, pp. 171–178, 2015.

[25] H. I. Kuo *et al.*, "Comparing cortical plasticity induced by conventional and high-definition 4 × 1 ring tDCS: A neurophysiological study," *Brain Stimulation*, 2013, doi: 10.1016/j.brs.2012.09.010.

[26] M. A. Nitsche *et al.*, "Transcranial direct current stimulation: State of the art 2008," *Brain*

Stimulation, vol. 1, no. 3, pp. 206–223, 2008.

[27] J. D. Power *et al.*, “Functional Network Organization of the Human Brain,” *Neuron*, vol. 72, no. 4, pp. 665–678, Nov. 2011, doi: 10.1016/j.neuron.2011.09.006.

[28] R. C. Kadosh, *The Stimulated Brain: Cognitive Enhancement Using Non-Invasive Brain Stimulation*. Waltham, MA: Academic Press, 2014.

[29] P. Y. Chhatbar and W. Feng, “Data synthesis in meta-analysis may conclude differently on cognitive effect from transcranial direct current stimulation,” *Brain Stimulation*, vol. 8, no. 5, pp. 974–976, 2015.

[30] A. T. Hill, P. B. Fitzgerald, and K. E. Hoy, “Effects of Anodal Transcranial Direct Current Stimulation on Working Memory: A Systematic Review and Meta-Analysis of Findings from Healthy and Neuropsychiatric Populations,” *Brain Stimulation*, vol. 9, no. 2, pp. 197–208, 2016, doi: 10.1016/j.brs.2015.10.006.

[31] J. C. Horvath, J. D. Forte, and O. Carter, “Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic review,” *Neuropsychologia*, vol. 66, pp. 213–236, 2015.

[32] J. C. Horvath, J. D. Forte, and O. Carter, “Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS),” *Brain Stimulation*, vol. 8, no. 3, pp. 535–550, 2015.

[33] L. E. Mancuso, I. P. Ilieva, R. H. Hamilton, and M. J. Farah, “Does transcranial direct current stimulation improve healthy working memory?: A meta-analytic review,” *Journal of Cognitive Neuroscience*, vol. 28, no. 8, pp. 1063–1089, 2016, doi: 10.1162/jocn_a_00956.

[34] J. Medina and S. Cason, “No evidential value in samples of transcranial direct current stimulation (tDCS) studies of cognition and working memory in healthy populations,” *Cortex*, vol. 94, pp. 131–141, Sep. 2017, doi: 10.1016/j.cortex.2017.06.021.

[35] L. Jacobson, M. Koslowsky, and M. Lavidor, “TDCS polarity effects in motor and cognitive domains: A meta-analytical review,” *Experimental Brain Research*, vol. 216, no. 1, pp. 1–10, 2012.

[36] F. Steinberg, N. H. Pixa, and F. Fregni, “A Review of Acute Aerobic Exercise and Transcranial Direct Current Stimulation Effects on Cognitive Functions and Their Potential Synergies,” *Front. Hum. Neurosci.*, vol. 12, 2019, doi: 10.3389/fnhum.2018.00534.

[37] S. Tremblay, J. F. Lepage, A. Latulipe-Loiselle, F. Fregni, A. Pascual-Leone, and H. Théoret, “The uncertain outcome of prefrontal tDCS,” *Brain Stimulation*, vol. 7, no. 6, pp. 773–783, 2014, doi: 10.1016/j.brs.2014.10.003.

[38] S. Bestmann, A. O. de Berker, and J. Bonaiuto, “Understanding the behavioural consequences of noninvasive brain stimulation,” *Trends in Cognitive Sciences*, vol. 19, no. 1, pp. 13–20, 2015.

[39] N. Ward *et al.*, “Enhanced Learning through Multimodal Training: Evidence from a Comprehensive Cognitive, Physical Fitness, and Neuroscience Intervention,” *Scientific Reports*, vol. 7, no. 1, Art. no. 1, Jul. 2017, doi: 10.1038/s41598-017-06237-5.

[40] M. E. Berryhill, E. B. Wencil, H. B. Coslett, and I. R. Olson, “A Selective Working Memory Impairment after Transcranial Direct Current Stimulation to the Right Parietal Lobe,” *Neurosci Lett*, vol. 479, no. 3, pp. 312–316, Aug. 2010, doi: 10.1016/j.neulet.2010.05.087.

[41] T. T. Brunyé, A. M. Smith, C. B. Horner, and A. K. Thomas, “Verbal long-term memory is enhanced by retrieval practice but impaired by prefrontal direct current stimulation,” *Brain and Cognition*, vol. 128, pp. 80–88, 2018.

[42] R. Matsushita, J. Andoh, and R. J. Zatorre, “Polarity-specific transcranial direct current stimulation disrupts auditory pitch learning,” *Front. Neurosci.*, vol. 9, 2015, doi: 10.3389/fnins.2015.00174.

[43] K. K. Sellers *et al.*, “Transcranial direct current stimulation (tDCS) of frontal cortex decreases performance on the WAIS-IV intelligence test,” *Behavioural Brain Research*, vol. 290, pp. 32–44, Sep. 2015, doi: 10.1016/j.bbr.2015.04.031.

[44] M. F. Tang and G. R. Hammond, “Anodal transcranial direct current stimulation over auditory cortex degrades frequency discrimination by affecting temporal, but not place, coding,” *European Journal of Neuroscience*, vol. 38, no. 5, pp. 2802–2811, 2013, doi: 10.1111/ejn.12280.

[45] A. Antal *et al.*, “Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and

application guidelines," *Clinical Neurophysiology*, vol. 128, no. 9, pp. 1774–1809, Sep. 2017, doi: 10.1016/j.clinph.2017.06.001.

[46] A. Wexler, "A pragmatic analysis of the regulation of consumer transcranial direct current stimulation (TDCS) devices in the United States," *Journal of Law and the Biosciences*, vol. 2, no. 3, pp. 669–696, Feb. 2016, doi: 10.1093/jlb/lsv039.

[47] A. Wexler, "Who uses direct-to-consumer brain stimulation products, and why? A study of home users of tDCS devices," *Journal of Cognitive Enhancement*, vol. 2, pp. 114–134, 2018.

[48] A. Wexler and P. B. Reiner, "Oversight of direct-to-consumer neurotechnologies," *Science*, vol. 363, no. 6424, pp. 234–235, Jan. 2019, doi: 10.1126/science.aav0223.

[49] M. Boudewyn, B. M. Roberts, E. Mizrak, C. Ranganath, and C. S. Carter, "Prefrontal Transcranial Direct Current Stimulation (tDCS) Enhances Behavioral and EEG Markers of Proactive Control," *Cogn Neurosci*, vol. 10, no. 2, pp. 57–65, 2019, doi: 10.1080/17588928.2018.1551869.

[50] T. T. Brunyé *et al.*, "Direct current brain stimulation enhances navigation efficiency in individuals with low spatial sense of direction," *NeuroReport*, vol. 25, no. 15, pp. 1175–1179, 2014, doi: 10.1097/WNR.0000000000000214.

[51] T. T. Brunyé, "Increasing breadth of semantic associations with left frontopolar direct current brain stimulation: a role for individual differences.," *Neuroreport*, vol. 26, no. 5, pp. 296–301, 2015.

[52] T. T. Brunyé, E. K. Hussey, A. L. Gardony, A. Holmes, and H. A. Taylor, "Targeted right medial temporal lobe tDCS and associative spatial and non-spatial memory," *Journal of Cognitive Enhancement*, vol. 3, pp. 287–297, 2018.

[53] N. Kaur *et al.*, "Targeting the anterior cingulate with bipolar and high-definition transcranial direct current stimulation," *NeuroReport*, vol. 31, pp. 346–351, 2020.

[54] L. K. McIntire, R. A. McKinley, C. Goodyear, and J. M. Nelson, "A comparison of the effects of transcranial direct current stimulation and caffeine on vigilance and cognitive performance during extended wakefulness," *Brain Stimulation*, vol. 7, pp. 499–507, 2014.

[55] R. A. McKinley, L. McIntire, N. Bridges, C. Goodyear, and M. P. Weisend, "Acceleration of image analyst training with transcranial direct current stimulation," *Behavioral Neuroscience*, vol. 127, pp. 936–946, 2013.

[56] E. Mizrak, K. Kim, B. Roberts, D. J. Ragland, C. Carter, and C. Ranganath, "Impact of oscillatory tDCS targeting left prefrontal cortex on source memory retrieval," *Cognitive Neuroscience*, vol. 9, no. 3–4, pp. 194–207, Oct. 2018, doi: 10.1080/17588928.2018.1512480.

[57] J. T. Nelson, R. A. McKinley, E. J. Golob, J. S. Warm, and R. Parasuraman, "Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS)," *NeuroImage*, vol. 85, pp. 909–917, 2014.

[58] J. M. Nelson, R. A. McKinley, L. K. McIntire, C. Goodyear, and C. Walters, "Augmenting visual search performance with transcranial direct current stimulation (tDCS)," *Military Psychology*, vol. 27, no. 6, pp. 335–347, 2015, doi: 10.1037/mil0000085.

[59] J. T. Nelson *et al.*, "The effects of transcranial direct current stimulation (tDCS) on multitasking throughput capacity," *Frontiers in Human Neuroscience*, vol. 10, pp. 589–589, 2016.

[60] R. Parasuraman and R. A. McKinley, "Using noninvasive brain stimulation to accelerate learning and enhance human performance," *Human Factors*, vol. 56, pp. 816–824, 2014.

[61] J. Kubanek, "Neuromodulation with transcranial focused ultrasound," *Neurosurgical Focus*, vol. 44, no. 2, p. E14, Feb. 2018, doi: 10.3171/2017.11.FOCUS17621.

[62] F. J. Fry, H. W. Ades, and W. J. Fry, "Production of Reversible Changes in the Central Nervous System by Ultrasound," *Science*, vol. 127, no. 3289, pp. 83–84, Jan. 1958, doi: 10.1126/science.127.3289.83.

[63] D. Folloni *et al.*, "Manipulation of Subcortical and Deep Cortical Activity in the Primate Brain Using Transcranial Focused Ultrasound Stimulation," *Neuron*, vol. 101, no. 6, pp. 1109-1116.e5, Mar. 2019, doi: 10.1016/j.neuron.2019.01.019.

[64] V. Krishna, F. Sammartino, and A. Rezai, "A Review of the Current Therapies, Challenges, and Future Directions of Transcranial Focused Ultrasound Technology: Advances in Diagnosis and Treatment," *JAMA neurology*, vol. 75, no. 2, pp. 246–254, 01 2018, doi:

10.1001/jamaneurol.2017.3129.

[65] W. Legon *et al.*, “Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans,” *Nature Neuroscience*, vol. 17, no. 2, Art. no. 2, Feb. 2014, doi: 10.1038/nn.3620.

[66] W. Lee, H. Kim, Y. Jung, I.-U. Song, Y. A. Chung, and S.-S. Yoo, “Image-Guided Transcranial Focused Ultrasound Stimulates Human Primary Somatosensory Cortex,” *Scientific Reports*, vol. 5, no. 1, Art. no. 1, Mar. 2015, doi: 10.1038/srep08743.

[67] J. Mueller, W. Legon, A. Opitz, T. F. Sato, and W. J. Tyler, “Transcranial focused ultrasound modulates intrinsic and evoked EEG dynamics,” *Brain Stimulation*, vol. 7, no. 6, pp. 900–908, Dec. 2014, doi: 10.1016/j.brs.2014.08.008.

[68] W. Lee *et al.*, “Transcranial focused ultrasound stimulation of human primary visual cortex,” *Scientific Reports*, vol. 6, no. 1, Art. no. 1, Sep. 2016, doi: 10.1038/srep34026.

[69] W. Legon, L. Ai, P. Bansal, and J. K. Mueller, “Neuromodulation with single-element transcranial focused ultrasound in human thalamus,” *Human Brain Mapping*, vol. 39, no. 5, pp. 1995–2006, 2018, doi: 10.1002/hbm.23981.

[70] C. Pasquinelli, L. G. Hanson, H. R. Siebner, H. J. Lee, and A. Thielscher, “Safety of transcranial focused ultrasound stimulation: A systematic review of the state of knowledge from both human and animal studies,” *Brain Stimulation*, vol. 12, no. 6, pp. 1367–1380, Nov. 2019, doi: 10.1016/j.brs.2019.07.024.

[71] L. S. Colzato and K. Vonck, “Transcutaneous vagus and trigeminal nerve stimulation,” in *Theory-Driven Approaches to Cognitive Enhancement*, L. S. Colzato, Ed. Cham: Springer, 2017, pp. 115–126.

[72] B. W. Badran *et al.*, “Neurophysiologic effects of transcutaneous auricular vagus nerve stimulation (taVNS) via electrical stimulation of the tragus: A concurrent taVNS/fMRI study and review,” *Brain Stimulation*, vol. 11, pp. 492–500, 2018, doi: 10.1016/j.brs.2017.12.009.

[73] W. J. Tyler *et al.*, “Transdermal neuromodulation of noradrenergic activity suppresses psychophysiological and biochemical stress responses in humans,” *Scientific Reports*, vol. 5, pp. 13865–13865, Sep. 2015, doi: 10.1038/srep13865.

[74] R. Sellaro, J. W. R. van Leusden, K. D. Tona, B. Verkuil, S. Nieuwenhuis, and L. S. Colzato, “Transcutaneous vagus nerve stimulation enhances post-error slowing,” *Journal of Cognitive Neuroscience*, vol. 27, no. 11, pp. 2126–2132, Nov. 2015, doi: 10.1162/jocn_a_00851.

[75] H. Jacobs, J. M. Riphagen, C. M. Razat, S. Wiese, and A. T. Sack, “Transcutaneous vagus nerve stimulation boosts associative memory in older individuals,” *Neurobiology of Aging*, vol. 36, no. 5, pp. 1860–1867, 2015, doi: 10.1016/j.neurobiolaging.2015.02.023.

[76] A. M. Burger, B. Verkuil, I. Van Diest, W. Van der Does, J. F. Thayer, and J. F. Brosschot, “The effects of transcutaneous vagus nerve stimulation on conditioned fear extinction in humans,” *Neurobiology of Learning and Memory*, vol. 132, pp. 49–56, Jul. 2016, doi: 10.1016/j.nlm.2016.05.007.

[77] L. S. Colzato, S. M. Ritter, and L. Steenbergen, “Transcutaneous vagus nerve stimulation (tVNS) enhances divergent thinking,” *Neuropsychologia*, vol. 111, pp. 72–76, 2018, doi: 10.1016/j.neuropsychologia.2018.01.003.

[78] L. Steenbergen, R. Sellaro, A. K. Stock, B. Verkuil, C. Beste, and L. S. Colzato, “Transcutaneous vagus nerve stimulation (tVNS) enhances response selection during action cascading processes,” *European Neuropsychopharmacology*, vol. 25, pp. 773–778, 2015, doi: 10.1016/j.euroneuro.2015.03.015.

[79] J. A. Clancy, D. A. Mary, K. K. Witte, J. P. Greenwood, S. A. Deuchars, and J. Deuchars, “Non-invasive Vagus Nerve Stimulation in Healthy Humans Reduces Sympathetic Nerve Activity,” *Brain Stimulation*, vol. 7, no. 6, pp. 871–877, Nov. 2014, doi: 10.1016/j.brs.2014.07.031.

[80] M. Usher, J. D. Cohen, D. Servan-Schrieber, J. Rajkowski, and G. Aston-Jones, “The Role of Locus Coeruleus in the Regulation of Cognitive Performance,” *Science*, vol. 283, no. 5401, pp. 549–554, Jan. 1999, doi: 10.1126/science.283.5401.549.

[81] G. Aston-Jones and J. D. Cohen, “An integrative theory of locus coeruleus-norepinephrine

function: adaptive gain and optimal performance.," *Annual review of neuroscience*, vol. 28, pp. 403–450, 2005, doi: 10.1146/annurev.neuro.28.061604.135709.

[82] S. Birnbaum, K. T. Gobeske, J. Auerbach, J. R. Taylor, and A. F. Arnsten, "A role for norepinephrine in stress-induced cognitive deficits: alpha-1-adrenoceptor mediation in the prefrontal cortex," *Biol Psychiatry*, vol. 46, no. 9, pp. 1266–1274, Nov. 1999, doi: 10.1016/s0006-3223(99)00138-9.

[83] J. I. Friedman, D. N. Adler, and K. L. David, "The role of norepinephrine in the pathophysiology of cognitive disorders: Potential applications to the treatment of cognitive dysfunction in schizophrenia and Alzheimer's disease," *Biological Psychiatry*, vol. 46, no. 9, pp. 1243–1252, 1999, doi: 10.1016/S0006-3223(99)00232-2.

[84] J. Grant, *An Atlas of Anatomy*, 6th ed. Baltimore, MD: Williams & Wilkins, 1972.

[85] J. J. McGough *et al.*, "Double-Blind, Sham-Controlled, Pilot Study of Trigeminal Nerve Stimulation for Attention-Deficit/Hyperactivity Disorder," *Journal of the American Academy of Child & Adolescent Psychiatry*, vol. 58, no. 4, pp. 403-411.e3, Apr. 2019, doi: 10.1016/j.jaac.2018.11.013.

[86] P. Shiozawa *et al.*, "Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis.," *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*, vol. 17, no. 9, pp. 1443–52, Sep. 2014, doi: 10.1017/S1461145714000418.

[87] D. Magis *et al.*, "Cerebral metabolism before and after external trigeminal nerve stimulation in episodic migraine," *Cephalalgia*, vol. 37, no. 9, pp. 881–891, Aug. 2017, doi: 10.1177/0333102416656118.

[88] C. M. DeGiorgio, D. Murray, D. Markovic, and T. Whitehurst, "Trigeminal nerve stimulation for epilepsy: long-term feasibility and efficacy," *Neurology*, vol. 72, no. 10, pp. 936–938, Mar. 2009, doi: 10.1212/01.wnl.0000344181.97126.b4.

[89] J. D. Feusner *et al.*, "Effects of cranial electrotherapy stimulation on resting state brain activity," *Brain Behav*, vol. 2, no. 3, pp. 211–220, May 2012, doi: 10.1002/brb3.45.

[90] P. G. Shekelle, I. A. Cook, I. M. Miake-Lye, M. S. Booth, J. M. Beroes, and S. Mak, "Benefits and Harms of Cranial Electrical Stimulation for Chronic Painful Conditions, Depression, Anxiety, and Insomnia," *Annals of Internal Medicine*, vol. 168, no. 6, pp. 414–421, Feb. 2018, doi: 10.7326/M17-1970.

[91] P. G. Shekelle *et al.*, "The Effectiveness and Risks of Cranial Electrical Stimulation for the Treatment of Pain, Depression, Anxiety, PTSD, and Insomnia: A Systematic Review," Department of Veterans Affairs, VA ESP Project #05-226, 2018.

[92] L. Cupriks, V. Vimbsons, A. Cuprika, and A. Rudzitis, "Cranial electrical stimulation in fitness with weightlifting tools," *LASE Journal of Sport Science*, vol. 7, pp. 21–32, 2016.

[93] O. N. Koleoso, H. O. Osinowo, and K. O. Akhigbe, "The role of relaxation therapy and cranial electrotherapy stimulation in the management of dental anxiety in Nigeria," *IOSR Journal of Dental and Medical Sciences*, vol. 10, pp. 51–57, 2013.

[94] S. Southworth, "A study of the effects of cranial electrical stimulation on attention and concentration," *Integr Physiol Behav Sci*, vol. 34, no. 1, pp. 43–53, Mar. 1999, doi: 10.1007/BF02688709.

[95] B. Wagenseil, C. Garcia, A. V. Suvorov, I. Fietze, and T. Penzel, "The effect of cranial electrotherapy stimulation on sleep in healthy women," *Physiol. Meas.*, vol. 39, no. 11, p. 114007, Nov. 2018, doi: 10.1088/1361-6579/aaeafa.

[96] R. L. Winick, "Cranial electrotherapy stimulation (CES): a safe and effective low cost means of anxiety control in a dental practice," *Gen Dent*, vol. 47, no. 1, pp. 50–55, Feb. 1999.

[97] L. Black *et al.*, "Student Scholarship Presentation Abstracts, Journal of Neurotherapy: Investigations in Neuromodulation, Neurofeedback and Applied Neuroscience," *Journal of Neurotherapy*, vol. 8, no. 2, pp. 107–118, 2004.

[98] A. Datta, J. P. Dmochowski, B. Guleyupoglu, M. Bikson, and F. Fregni, "Cranial electrotherapy stimulation and transcranial pulsed current stimulation: A computer based high-resolution

modeling study," *NeuroImage*, vol. 65, pp. 280–287, Jan. 2013, doi: 10.1016/j.neuroimage.2012.09.062.

[99] M. Ferdjallah, F. X. Bostick, and R. E. Barr, "Potential and current density distributions of cranial electrotherapy stimulation (CES) in a four-concentric-spheres model," *IEEE Transactions on Biomedical Engineering*, vol. 43, no. 9, pp. 939–943, Sep. 1996, doi: 10.1109/10.532128.

[100] D. Gense de Beaufort, M. Sesay, L. Stinus, R. Thiebaut, M. Auriacombe, and V. Dousset, "Cerebral blood flow modulation by transcutaneous cranial electrical stimulation with Limoge's current," *Journal of Neuroradiology*, vol. 39, no. 3, pp. 167–175, Jul. 2012, doi: 10.1016/j.neurad.2011.06.001.

[101] B. Lee, Y. J. N. Lee, S. Park, H. Kim, S. J. Lee, and J. Kim, "Driver's distraction and understandability (EOU) change due to the level of abstractness and modality of GPS navigation information during driving," in *Procedia Computer Science*, 2014, vol. 39, no. C, pp. 115–122. doi: 10.1016/j.procs.2014.11.017.

[102] M. J. Schroeder and R. E. Barr, "Quantitative analysis of the electroencephalogram during cranial electrotherapy stimulation," *Clinical Neurophysiology*, vol. 112, no. 11, pp. 2075–2083, Nov. 2001, doi: 10.1016/S1388-2457(01)00657-5.

[103] R. Sitaram *et al.*, "Closed-loop brain training: the science of neurofeedback," *Nature Reviews Neuroscience*, vol. 18, no. 2, Art. no. 2, Feb. 2017, doi: 10.1038/nrn.2016.164.

[104] S. T. Foldes, D. J. Weber, and J. L. Collinger, "MEG-based neurofeedback for hand rehabilitation," *J Neuroeng Rehabil*, vol. 12, Sep. 2015, doi: 10.1186/s12984-015-0076-7.

[105] T. Renton, A. Tibbles, and J. Topolovec-Vranic, "Neurofeedback as a form of cognitive rehabilitation therapy following stroke: A systematic review," *PLoS One*, vol. 12, no. 5, May 2017, doi: 10.1371/journal.pone.0177290.

[106] K. Mayer, S. N. Wyckoff, A. J. Fallgatter, A.-C. Ehlis, and U. Strehl, "Neurofeedback as a nonpharmacological treatment for adults with attention-deficit/hyperactivity disorder (ADHD): study protocol for a randomized controlled trial," *Trials*, vol. 16, Apr. 2015, doi: 10.1186/s13063-015-0683-4.

[107] M. T. deBettencourt, J. D. Cohen, R. F. Lee, K. A. Norman, and N. B. Turk-Browne, "Closed-loop training of attention with real-time brain imaging," *Nature Neuroscience*, vol. 18, no. 3, Art. no. 3, Mar. 2015, doi: 10.1038/nn.3940.

[108] E. Dessy, M. Van Puyvelde, O. Mairesse, X. Neyt, and N. Pattyn, "Cognitive Performance Enhancement: Do Biofeedback and Neurofeedback Work?," *J Cogn Enhanc*, vol. 2, no. 1, pp. 12–42, Mar. 2018, doi: 10.1007/s41465-017-0039-y.

[109] S. Enriquez-Geppert, R. J. Huster, and C. S. Herrmann, "EEG-Neurofeedback as a Tool to Modulate Cognition and Behavior: A Review Tutorial," *Front Hum Neurosci*, vol. 11, Feb. 2017, doi: 10.3389/fnhum.2017.00051.

[110] J. H. Gruzelier, "EEG-neurofeedback for optimising performance. I: a review of cognitive and affective outcome in healthy participants," *Neurosci Biobehav Rev*, vol. 44, pp. 124–141, Jul. 2014, doi: 10.1016/j.neubiorev.2013.09.015.

[111] F. Scharnowski and N. Weiskopf, "Cognitive enhancement through real-time fMRI neurofeedback," *Current Opinion in Behavioral Sciences*, vol. 4, pp. 122–127, Aug. 2015, doi: 10.1016/j.cobeha.2015.05.001.

[112] M. Ninaus *et al.*, "Neural substrates of cognitive control under the belief of getting neurofeedback training," *Front. Hum. Neurosci.*, vol. 7, 2013, doi: 10.3389/fnhum.2013.00914.

[113] R. T. Thibault and A. Raz, "The psychology of neurofeedback: Clinical intervention even if applied placebo," *Am Psychol*, vol. 72, no. 7, pp. 679–688, Oct. 2017, doi: 10.1037/amp0000118.

[114] J. Faller, J. Cummings, S. Saproo, and P. Sajda, "Regulation of arousal via online neurofeedback improves human performance in a demanding sensory-motor task," *PNAS*, vol. 116, no. 13, pp. 6482–6490, Mar. 2019, doi: 10.1073/pnas.1817207116.

[115] D. S. Bassett and A. N. Khambhati, "A network engineering perspective on probing and perturbing cognition with neurofeedback," *Ann N Y Acad Sci*, vol. 1396, no. 1, pp. 126–143, May 2017, doi: 10.1111/nyas.13338.

[116] M. S. Sherwood, J. H. Kane, M. P. Weisend, and J. G. Parker, “Enhanced control of dorsolateral prefrontal cortex neurophysiology with real-time functional magnetic resonance imaging (rt-fMRI) neurofeedback training and working memory practice,” *NeuroImage*, vol. 124, pp. 214–223, Jan. 2016, doi: 10.1016/j.neuroimage.2015.08.074.

[117] M. S. Sherwood, M. P. Weisend, J. H. Kane, and J. G. Parker, “Combining Real-Time fMRI Neurofeedback Training of the DLPFC with N-Back Practice Results in Neuroplastic Effects Confined to the Neurofeedback Target Region,” *Front. Behav. Neurosci.*, vol. 10, 2016, doi: 10.3389/fnbeh.2016.00138.

[118] S. K. Kessler, P. E. Turkeltaub, J. G. Benson, and R. H. Hamilton, “Differences in the experience of active and sham transcranial direct current stimulation,” *Brain Stimulation*, vol. 5, no. 2, pp. 155–162, Apr. 2012, doi: 10.1016/j.brs.2011.02.007.

[119] J. Redgrave *et al.*, “Safety and tolerability of Transcutaneous Vagus Nerve stimulation in humans; a systematic review,” *Brain Stimulation*, vol. 11, no. 6, pp. 1225–1238, Nov. 2018, doi: 10.1016/j.brs.2018.08.010.

[120] G. G. Ambrus, W. Paulus, and A. Antal, “Cutaneous perception thresholds of electrical stimulation methods: comparison of tDCS and tRNS.,” *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*, vol. 121, no. 11, pp. 1908–14, Nov. 2010, doi: 10.1016/j.clinph.2010.04.020.

[121] M. Bikson *et al.*, “Safety of transcranial Direct Current Stimulation: Evidence Based Update 2016,” *Brain Stimul*, vol. 9, no. 5, pp. 641–661, 2016, doi: 10.1016/j.brs.2016.06.004.

[122] M. Bikson, A. Datta, and M. Elwassif, “Establishing safety limits for transcranial direct current stimulation,” *Clin Neurophysiol*, vol. 120, no. 6, pp. 1033–1034, Jun. 2009, doi: 10.1016/j.clinph.2009.03.018.

[123] S. Rossi *et al.*, “Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research,” *Clinical Neurophysiology*, vol. 120, pp. 2008–2039, 2009, doi: 10.1016/j.clinph.2009.08.016.

[124] C. K. Loo, T. F. McFarquhar, and P. B. Mitchell, “A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression,” *Int J Neuropsychopharmacol*, vol. 11, no. 1, pp. 131–147, Feb. 2008, doi: 10.1017/S1461145707007717.

[125] W. Legon *et al.*, “A retrospective qualitative report of symptoms and safety from transcranial focused ultrasound for neuromodulation in humans,” *Scientific Reports*, vol. 10, no. 1, Art. no. 1, Mar. 2020, doi: 10.1038/s41598-020-62265-8.

[126] D. L. Kirsch and F. Nichols, “Cranial electrotherapy stimulation for treatment of anxiety, depression, and insomnia,” *Psychiatr. Clin. North Am.*, vol. 36, no. 1, pp. 169–176, Mar. 2013, doi: 10.1016/j.psc.2013.01.006.

[127] D. L. Kirsch, L. R. Price, F. Nichols, J. A. Marksberry, and K. T. Platoni, “Military service member and veteran self reports of efficacy of cranial electrotherapy stimulation for anxiety, posttraumatic stress disorder, insomnia, and depression,” *US Army Med Dep J*, pp. 46–54, Dec. 2014.

[128] D. McClure, S. C. Greenman, S. S. Koppolu, M. Varvara, Z. S. Yaseen, and I. I. Galynker, “A Pilot Study of Safety and Efficacy of Cranial Electrotherapy Stimulation in Treatment of Bipolar II Depression,” *J Nerv Ment Dis*, vol. 203, no. 11, pp. 827–835, Nov. 2015, doi: 10.1097/NMD.0000000000000378.

[129] D. Mischoulon *et al.*, “Efficacy and safety of a form of cranial electrical stimulation (CES) as an add-on intervention for treatment-resistant major depressive disorder: A three week double blind pilot study,” *Journal of Psychiatric Research*, vol. 70, pp. 98–105, Nov. 2015, doi: 10.1016/j.jpsychires.2015.08.016.

[130] J. P. T. Higgins *et al.*, “The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials | The BMJ,” *BMJ*, vol. 343, p. d5928, 2011.

[131] C. Hotermans, P. Peigneux, A. M. D. Noordhout, G. Moonen, and P. Maquet, “Repetitive transcranial magnetic stimulation over the primary motor cortex disrupts early boost but not delayed gains in performance in motor sequence learning,” *European Journal of Neuroscience*, vol.

28, no. 6, pp. 1216–1221, 2008, doi: 10.1111/j.1460-9568.2008.06421.x.

[132] H. C. Kavirajan, K. Lueck, and K. Chuang, “Alternating current cranial electrotherapy stimulation (CES) for depression,” *Cochrane Database of Systematic Reviews*, no. 7, 2014, doi: 10.1002/14651858.CD010521.pub2.

[133] N. E. O’Connell, B. M. Wand, L. Marston, S. Spencer, and L. H. Desouza, “Non-invasive brain stimulation techniques for chronic pain. A report of a Cochrane systematic review and meta-analysis,” *Eur J Phys Rehabil Med*, vol. 47, no. 2, pp. 309–326, Jun. 2011.

[134] F. Duecker and A. T. Sack, “Rethinking the role of sham TMS,” *Front. Psychol.*, vol. 6, 2015, doi: 10.3389/fpsyg.2015.00210.

[135] A. C. Conley, J. Marquez, M. W. Parsons, W. R. Fulham, A. Heathcote, and F. Karayanidis, “Anodal tDCS over the Motor Cortex on Prepared and Unprepared Responses in Young Adults,” *PLOS ONE*, vol. 10, no. 5, p. e0124509, May 2015, doi: 10.1371/journal.pone.0124509.

[136] K. Garrison, J. Santoyo, J. Davis, T. Thornhill, C. Kerr, and J. Brewer, “Effortless awareness: using real time neurofeedback to investigate correlates of posterior cingulate cortex activity in meditators’ self-report,” *Front. Hum. Neurosci.*, vol. 7, 2013, doi: 10.3389/fnhum.2013.00440.

[137] P. Mauri, C. Miniussi, M. Balconi, and D. Brignani, “Bursts of transcranial electrical stimulation increase arousal in a continuous performance test,” *Neuropsychologia*, vol. 74, pp. 127–136, 2015.

[138] T. Auer, R. Schweizer, and J. Frahm, “Training Efficiency and Transfer Success in an Extended Real-Time Functional MRI Neurofeedback Training of the Somatomotor Cortex of Healthy Subjects,” *Front. Hum. Neurosci.*, vol. 9, 2015, doi: 10.3389/fnhum.2015.00547.

[139] J. P. Hamilton, G. H. Glover, J. Hsu, R. F. Johnson, and I. H. Gotlib, “Modulation of subgenual anterior cingulate cortex activity with real-time neurofeedback,” *Hum Brain Mapp*, vol. 32, no. 1, pp. 22–31, Dec. 2010, doi: 10.1002/hbm.20997.

[140] S. M. Barnett and S. J. Ceci, “When and where do we apply what we learn? A taxonomy for far transfer,” *Psychological Bulletin*, vol. 128, no. 4, pp. 612–637, 2002, doi: 10.1037//0033-2909.128.4.612.

[141] T. T. Brunyé, A. M. Smith, D. Hendel, A. L. Gardony, S. B. Martis, and H. A. Taylor, “Retrieval practice enhances near but not far transfer of spatial memory,” *Journal of Experimental Psychology: Learning Memory and Cognition*, vol. 46, pp. 24–45, 2020, doi: 10.1037/xlm0000710.

[142] M. J. Imburgio and J. M. Orr, “Effects of prefrontal tDCS on executive function: Methodological considerations revealed by meta-analysis,” *Neuropsychologia*, vol. 117, pp. 156–166, Aug. 2018, doi: 10.1016/j.neuropsychologia.2018.04.022.

[143] C. D. Chambers, Z. Dienes, R. D. McIntosh, P. Rotshtein, and K. Willmes, “Registered reports: realigning incentives in scientific publishing,” *Cortex*, vol. 66, pp. A1-2, May 2015, doi: 10.1016/j.cortex.2015.03.022.

[144] S. E. Maxwell, M. Y. Lau, and G. S. Howard, “Is psychology suffering from a replication crisis? What does ‘failure to replicate’ really mean?,” *Am Psychol*, vol. 70, no. 6, pp. 487–498, Sep. 2015, doi: 10.1037/a0039400.

[145] J. P. A. Ioannidis, “Why Most Published Research Findings Are False,” *PLOS Medicine*, vol. 2, no. 8, p. e124, Aug. 2005, doi: 10.1371/journal.pmed.0020124.

[146] B. D. Earp and D. Trafimow, “Replication, falsification, and the crisis of confidence in social psychology,” *Front. Psychol.*, vol. 6, 2015, doi: 10.3389/fpsyg.2015.00621.

[147] J. W. Neuliep and R. Crandall, “Reviewer bias against replication research,” *Journal of Social Behavior & Personality*, vol. 8, no. 6, pp. 21–29, 1993.

[148] P. E. Meehl, “Why Summaries of Research on Psychological Theories are Often Uninterpretable,” *Psychol Rep*, vol. 66, no. 1, pp. 195–244, Feb. 1990, doi: 10.2466/pr0.1990.66.1.195.

[149] J. Protzko and J. W. Schooler, “Decline effects: Types, mechanisms, and personal reflections,” in *Psychological science under scrutiny: Recent challenges and proposed solutions*, Wiley-Blackwell, 2017, pp. 85–107. doi: 10.1002/9781119095910.ch6.

[150] J. Sulzer *et al.*, “Real-time fMRI neurofeedback: Progress and challenges,” *NeuroImage*, vol. 76, pp. 386–399, Aug. 2013, doi: 10.1016/j.neuroimage.2013.03.033.

[151] T. Boynton, “Applied Research Using Alpha/Theta Training for Enhancing Creativity and Well-

Being," *Journal of Neurotherapy*, vol. 5, no. 1–2, pp. 5–18, Oct. 2001, doi: 10.1300/J184v05n01_02.

[152] M. Schabus, H. Griessenberger, M.-T. Gnjezda, D. P. J. Heib, M. Wislowska, and K. Hoedlmoser, "Better than sham? A double-blind placebo-controlled neurofeedback study in primary insomnia," *Brain*, vol. 140, no. 4, pp. 1041–1052, Apr. 2017, doi: 10.1093/brain/awx011.

[153] P. Belardinelli *et al.*, "Reproducibility in TMS–EEG studies: A call for data sharing, standard procedures and effective experimental control," *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, vol. 12, no. 3, pp. 787–790, May 2019, doi: 10.1016/j.brs.2019.01.010.

[154] G.-J. Ji *et al.*, "Aftereffect and Reproducibility of Three Excitatory Repetitive TMS Protocols for a Response Inhibition Task," *Front. Neurosci.*, vol. 13, 2019, doi: 10.3389/fnins.2019.01155.

[155] M. C. Ridding and U. Ziemann, "Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects," *Journal of Physiology*, vol. 588, no. 13, pp. 2291–2304, Jul. 2010, doi: 10.1113/jphysiol.2010.190314.

[156] C. M. Warren *et al.*, "The neuromodulatory and hormonal effects of transcutaneous vagus nerve stimulation as evidenced by salivary alpha amylase, salivary cortisol, pupil diameter, and the P3 event-related potential," *Brain Stimulation*, vol. 12, no. 3, pp. 635–642, May 2019, doi: 10.1016/j.brs.2018.12.224.

[157] K. S. Button *et al.*, "Power failure: why small sample size undermines the reliability of neuroscience," *Nature Reviews Neuroscience*, vol. 14, no. 5, Art. no. 5, May 2013, doi: 10.1038/nrn3475.

[158] G. N. Martin and R. M. Clarke, "Are Psychology Journals Anti-replication? A Snapshot of Editorial Practices," *Front. Psychol.*, vol. 8, 2017, doi: 10.3389/fpsyg.2017.00523.

[159] J. Schooler, "Unpublished results hide the decline effect," *Nature*, vol. 470, no. 7335, Art. no. 7335, Feb. 2011, doi: 10.1038/470437a.

[160] G. Francis, "Publication bias and the failure of replication in experimental psychology," *Psychon Bull Rev*, vol. 19, no. 6, pp. 975–991, Dec. 2012, doi: 10.3758/s13423-012-0322-y.

[161] G. Thut and A. Pascual-Leone, "A Review of Combined TMS-EEG Studies to Characterize Lasting Effects of Repetitive TMS and Assess Their Usefulness in Cognitive and Clinical Neuroscience," *Brain Topogr*, vol. 22, no. 4, pp. 219–232, Jan. 2010, doi: 10.1007/s10548-009-0115-4.

[162] B. Lo and M. J. Field, *Conflict of Interest in Medical Research, Education, and Practice*. Washington, D. C.: National Academies Press, 2009.

[163] M. F. Gilula, "Cranial electrotherapy stimulation and fibromyalgia," *Expert Review of Medical Devices*, vol. 4, no. 4, pp. 489–495, Jul. 2007, doi: 10.1586/17434440.4.4.489.

[164] D. L. Kirsch and S. C. Chan, "Microcurrent and cranial electrotherapy stimulator for control of anxiety, insomnia, depression and pain," US8612008B2, Dec. 17, 2013

[165] D. L. Kirsch and M. F. Gilula, "CES in the treatment of depression, part 2," *Practical Pain Management*, vol. 6, pp. 32–40, 2007.

[166] D. L. Kirsch and R. B. Smith, "The use of cranial electrotherapy stimulation in the management of chronic pain: A review," *NeuroRehabilitation*, vol. 14, pp. 85–94, 2000.

[167] A. Chatterjee, "Chapter 27 - The ethics of neuroenhancement," in *Handbook of Clinical Neurology*, vol. 118, J. L. Bernat and H. R. Beresford, Eds. Elsevier, 2013, pp. 323–334. doi: 10.1016/B978-0-444-53501-6.00027-5.

[168] T. L. Beauchamp, "Methods and principles in biomedical ethics," *Journal of Medical Ethics*, vol. 29, no. 5, pp. 269–274, Oct. 2003, doi: 10.1136/jme.29.5.269.

[169] T. Beauchamp, "The Principle of Beneficence in Applied Ethics," in *The Stanford Encyclopedia of Philosophy*, Stanford, CA: Stanford University, 2019.

[170] M. B. Russo, M. C. Stetz, and T. A. Stetz, "Brain enhancement in the military," in *Neuroethics in Practice: Medicine, mind, and society*, New York, NY: Oxford University Press, 2013, pp. 35–45.

[171] A. L. Caplan, "Is better best? A noted ethicist argues in favor of brain enhancement," *Sci Am*, vol. 289, no. 3, pp. 104–105, Sep. 2003.

[172] M. Wade, “Virtuous Play: The Ethics, Pleasures, and Burdens of Brain Training,” *Science as Culture*, vol. 27, no. 3, pp. 296–321, Jul. 2018, doi: 10.1080/09505431.2018.1458828.

[173] R. Goodman, “Cognitive enhancement, cheating, and accomplishment,” *Kennedy Inst Ethics J*, vol. 20, no. 2, pp. 145–160, Jun. 2010, doi: 10.1353/ken.0.0309.

[174] V. Dubljević, “Neurostimulation Devices for Cognitive Enhancement: Toward a Comprehensive Regulatory Framework,” *Neuroethics*, vol. 8, no. 2, pp. 115–126, Aug. 2015, doi: 10.1007/s12152-014-9225-0.

[175] B. Luber, “Neuroenhancement by noninvasive brain stimulation is not a net zero-sum proposition,” *Front Syst Neurosci*, vol. 8, Jul. 2014, doi: 10.3389/fnsys.2014.00127.

[176] N. U. F. Dosenbach, D. A. Fair, A. L. Cohen, B. L. Schlaggar, and S. E. Petersen, “A dual-networks architecture of top-down control,” *Trends in Cognitive Sciences*, vol. 12, no. 3, pp. 99–105, Mar. 2008, doi: 10.1016/j.tics.2008.01.001.

[177] T. P. Zanto and A. Gazzaley, “Fronto-parietal network: flexible hub of cognitive control,” *Trends Cogn Sci*, vol. 17, no. 12, Dec. 2013, doi: 10.1016/j.tics.2013.10.001.

[178] T. Chen, W. Cai, S. Ryali, K. Supekar, and V. Menon, “Distinct Global Brain Dynamics and Spatiotemporal Organization of the Salience Network,” *PLOS Biology*, vol. 14, no. 6, p. e1002469, Jun. 2016, doi: 10.1371/journal.pbio.1002469.

[179] N. Agar, *Truly Human Enhancement: A Philosophical Defense of Limits*. MIT Press, 2013.

[180] W. H. Teichner, “Recent studies of simple reaction time,” *Psychological Bulletin*, vol. 51, no. 2, pp. 128–149, 1954, doi: 10.1037/h0060900.

[181] L. Henderson and W. H. Dittrich, “Preparing to react in the absence of uncertainty: I. New perspectives on simple reaction time,” *Br J Psychol*, vol. 89 (Pt 4), pp. 531–554, Nov. 1998, doi: 10.1111/j.2044-8295.1998.tb02702.x.

[182] C. D. Wickens, “Temporal limits of human information processing: A developmental study,” *Psychological Bulletin*, vol. 81, no. 11, pp. 739–755, 1974, doi: 10.1037/h0037250.

[183] H. Takemura, K. Yuasa, and K. Amano, “Predicting Neural Response Latency of the Human Early Visual Cortex from MRI-Based Tissue Measurements of the Optic Radiation,” *eNeuro*, vol. 7, no. 4, Jul. 2020, doi: 10.1523/ENEURO.0545-19.2020.

[184] R. Cantello, C. Civardi, A. Cavalli, C. Varrasi, and R. Vicentini, “Effects of a photic input on the human cortico-motoneuron connection,” *Clinical Neurophysiology*, vol. 111, no. 11, pp. 1981–1989, Nov. 2000, doi: 10.1016/S1388-2457(00)00431-4.

[185] K. Sugawara *et al.*, “Activation of the human premotor cortex during motor preparation in visuomotor tasks,” *Brain Topogr*, vol. 26, no. 4, pp. 581–590, Oct. 2013, doi: 10.1007/s10548-013-0299-5.

[186] W. H. Teichner and M. J. Krebs, “Laws of visual choice reaction time,” *Psychological Review*, vol. 81, no. 1, pp. 75–98, 1974, doi: 10.1037/h0035867.

[187] D. R. J. Laming, *Information theory of choice-reaction times*. London, UK: Academic Press, 1968.

[188] D. L. Woods, J. M. Wyma, E. W. Yund, T. J. Herron, and B. Reed, “Factors influencing the latency of simple reaction time,” *Front. Hum. Neurosci.*, vol. 9, 2015, doi: 10.3389/fnhum.2015.00131.

[189] N. Kida, S. Oda, and M. Matsumura, “Intensive baseball practice improves the Go/Nogo reaction time, but not the simple reaction time,” *Cognitive Brain Research*, vol. 22, no. 2, pp. 257–264, Feb. 2005, doi: 10.1016/j.cogbrainres.2004.09.003.

[190] R. Langner, M. B. Steinborn, A. Chatterjee, W. Sturm, and K. Willmes, “Mental fatigue and temporal preparation in simple reaction-time performance,” *Acta Psychologica*, vol. 133, no. 1, pp. 64–72, Jan. 2010, doi: 10.1016/j.actpsy.2009.10.001.

[191] B. Forster, C. Cavina-Pratesi, S. M. Aglioti, and G. Berlucchi, “Redundant target effect and intersensory facilitation from visual-tactile interactions in simple reaction time,” *Exp Brain Res*, vol. 143, no. 4, pp. 480–487, Apr. 2002, doi: 10.1007/s00221-002-1017-9.

[192] J. O. Miller and K. Low, “Motor processes in simple, go/no-go, and choice reaction time tasks: A psychophysiological analysis,” *Journal of Experimental Psychology: Human Perception and Performance*, vol. 27, no. 2, pp. 266–289, 2001, doi: 10.1037/0096-1523.27.2.266.

[193] A. Egoyan and I. Khipashvili, “Use of psychophysiological computer tests during the process of

sportsmen's preparation," *Physical Education, Sport, Science*, vol. 2, no. 3, pp. 8–17, 2017.

[194] L. R. Duncan and V. S. Thomas, *Response Times: their Role in Inferring Elementary Mental Organization*. New York, NY: Oxford University Press, 1991.

[195] J. Miller, "Divided attention: evidence for coactivation with redundant signals," *Cogn Psychol*, vol. 14, no. 2, pp. 247–279, Apr. 1982, doi: 10.1016/0010-0285(82)90010-x.

[196] G. Batsikadze, V. Moliadze, W. Paulus, M.-F. M.-F. Kuo, and M. A. Nitsche, "Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans," *The Journal of physiology*, vol. 591, no. 7, pp. 1987–2000, Apr. 2013, doi: 10.1113/jphysiol.2012.249730.

[197] K. Monte-Silva *et al.*, "Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation.," *Brain stimulation*, vol. 6, no. 3, pp. 424–32, May 2013, doi: 10.1016/j.brs.2012.04.011.

[198] J. P. Dmochowski, M. Bikson, A. Datta, J. Richardson, J. Fridriksson, and L. C. Parra, "On the role of electric field orientation in optimal design of transcranial current stimulation," in *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*, 2012, pp. 6426–6429. doi: 10.1109/EMBC.2012.6347465.

[199] D. Tranchina and C. Nicholson, "A model for the polarization of neurons by extrinsically applied electric fields," *Biophysical Journal*, vol. 50, pp. 1139–1156, 1986, doi: 10.1016/S0006-3495(86)83558-5.

[200] J. J. Bonaiuto and S. Bestmann, "Understanding the nonlinear physiological and behavioral effects of tDCS through computational neurostimulation," *Progress in Brain Research*, vol. 222, pp. 75–103, 2015, doi: 10.1016/bs.pbr.2015.06.013.

[201] A. Lackmy-Vallee, L.-S. Giboin, and V. Marchand-Pauvert, "Non-linear input-output properties of the cortical networks mediating TMS-induced short-interval intracortical inhibition in humans," *Eur J Neurosci*, vol. 35, no. 3, pp. 457–467, Feb. 2012, doi: 10.1111/j.1460-9568.2011.07961.x.

[202] M. Bikson, A. Rahman, and A. Datta, "Computational models of transcranial direct current stimulation," *Clin EEG Neurosci*, vol. 43, no. 3, pp. 176–183, Jul. 2012, doi: 10.1177/1550059412445138.

[203] J. L. Alford, P. van Donkelaar, P. Dassonville, and R. T. Marrocco, "Transcranial magnetic stimulation over MT/MST fails to impair judgments of implied motion," *Cogn Affect Behav Neurosci*, vol. 7, no. 3, pp. 225–232, Sep. 2007, doi: 10.3758/cabn.7.3.225.

[204] C. C. Hilgetag, H. Théoret, and A. Pascual-Leone, "Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex," *Nat Neurosci*, vol. 4, no. 9, pp. 953–957, Sep. 2001, doi: 10.1038/nn0901-953.

[205] G. Thut, A. Nietzel, and A. Pascual-Leone, "Dorsal posterior parietal rTMS affects voluntary orienting of visuospatial attention," *Cereb. Cortex*, vol. 15, no. 5, pp. 628–638, May 2005, doi: 10.1093/cercor/bhh164.

[206] G. Hayward, G. M. Goodwin, and C. J. Harmer, "The role of the anterior cingulate cortex in the counting Stroop task," *Exp Brain Res*, vol. 154, no. 3, pp. 355–358, Feb. 2004, doi: 10.1007/s00221-003-1665-4.

[207] T. T. Brunyé, E. K. Hussey, E. B. Fontes, and N. Ward, "Modulating applied task performance via transcranial electrical stimulation," *Frontiers in Human Neuroscience*, vol. 13, pp. 140–140, 2019.

[208] S. Stanslaski *et al.*, "Design and validation of a fully implantable, chronic, closed-loop neuromodulation device with concurrent sensing and stimulation," *IEEE Trans Neural Syst Rehabil Eng*, vol. 20, no. 4, pp. 410–421, Jul. 2012, doi: 10.1109/TNSRE.2012.2183617.

[209] F. T. Sun and M. J. Morrell, "Closed-loop neurostimulation: the clinical experience," *Neurotherapeutics*, vol. 11, no. 3, pp. 553–563, Jul. 2014, doi: 10.1007/s13311-014-0280-3.

[210] J. Choi, M. Kwon, and S. C. Jun, "A Systematic Review of Closed-Loop Feedback Techniques in Sleep Studies-Related Issues and Future Directions," *Sensors (Basel)*, vol. 20, no. 10, May 2020, doi: 10.3390/s20102770.

[211] N. Ketz, A. P. Jones, N. B. Bryant, V. P. Clark, and P. K. Pilly, "Closed-Loop Slow-Wave tACS Improves Sleep-Dependent Long-Term Memory Generalization by Modulating Endogenous

Oscillations," *J Neurosci*, vol. 38, no. 33, pp. 7314–7326, Aug. 2018, doi: 10.1523/JNEUROSCI.0273-18.2018.

[212] Y. Zhang and R. Gruber, "Can Slow-Wave Sleep Enhancement Improve Memory? A Review of Current Approaches and Cognitive Outcomes," *Yale J Biol Med*, vol. 92, no. 1, pp. 63–80, Mar. 2019.

[213] G. Li and W. Chung, "Combined EEG-Gyroscope-tDCS Brain Machine Interface System for Early Management of Driver Drowsiness," *IEEE Transactions on Human-Machine Systems*, vol. 48, no. 1, pp. 50–62, Feb. 2018, doi: 10.1109/THMS.2017.2759808.

[214] R. A. McKinley, N. Bridges, C. M. Walters, and J. Nelson, "Modulating the brain at work using noninvasive transcranial stimulation," *Neuroimage*, vol. 59, no. 1, pp. 129–137, Jan. 2012, doi: 10.1016/j.neuroimage.2011.07.075.

[215] J. Silvanto, N. Muggleton, and V. Walsh, "State-dependency in brain stimulation studies of perception and cognition," *Trends in Cognitive Sciences*, vol. 12, no. 12, pp. 447–454, Dec. 2008, doi: 10.1016/j.tics.2008.09.004.

[216] A. Zhou, B. C. Johnson, and R. Muller, "Toward true closed-loop neuromodulation: artifact-free recording during stimulation," *Curr Opin Neurobiol*, vol. 50, pp. 119–127, 2018, doi: 10.1016/j.conb.2018.01.012.

[217] M. A. Nitsche, H. Knotkova, A. J. Woods, and M. Bikson, "Challenges, Open Questions and Future Direction in Transcranial Direct Current Stimulation Research and Applications," in *Practical Guide to Transcranial Direct Current Stimulation: Principles, Procedures and Applications*, H. Knotkova, M. A. Nitsche, M. Bikson, and A. J. Woods, Eds. Cham: Springer International Publishing, 2019, pp. 627–639. doi: 10.1007/978-3-319-95948-1_21.

[218] A. Bastani and S. Jaberzadeh, "Within-session repeated a-tDCS: the effects of repetition rate and inter-stimulus interval on corticospinal excitability and motor performance," *Clin Neurophysiol*, vol. 125, no. 9, pp. 1809–1818, Sep. 2014, doi: 10.1016/j.clinph.2014.01.010.

[219] J. R. Behrens, A. Kraft, K. Irlbacher, H. Gerhardt, M. C. Olma, and S. A. Brandt, "Long-Lasting Enhancement of Visual Perception with Repetitive Noninvasive Transcranial Direct Current Stimulation," *Front Cell Neurosci*, vol. 11, Aug. 2017, doi: 10.3389/fncel.2017.00238.

[220] A. Jamil *et al.*, "Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation," *J Physiol*, vol. 595, no. 4, pp. 1273–1288, Feb. 2017, doi: 10.1113/JP272738.

[221] M. A. Nitsche and W. Paulus, "Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans," *Neurology*, vol. 57, no. 10, pp. 1899–1901, Nov. 2001, doi: 10.1212/WNL.57.10.1899.

[222] K. Monte-Silva, M.-F. Kuo, D. Liebetanz, W. Paulus, and M. A. Nitsche, "Shaping the Optimal Repetition Interval for Cathodal Transcranial Direct Current Stimulation (tDCS)," *Journal of Neurophysiology*, vol. 103, no. 4, pp. 1735–1740, Jan. 2010, doi: 10.1152/jn.00924.2009.

AUTHOR BIOGRAPHIES

Tad T. Brunyé is a Senior Cognitive Scientist at the U.S. Army DEVCOM Soldier Center in Natick, MA. He also holds positions as Scientific Manager at the Center for Applied Brain and Cognitive Sciences, and Visiting Associate Professor in the Department of Psychology at Tufts University in Medford, MA, USA.

Monique E. Beaudoin is an Associate Research Scientist at the Applied Research Laboratory for Intelligence and Security (ARLIS) at the University of Maryland at College Park, USA.

Kathryn A. Feltman is a Research Psychologist at the U.S. Army Aeromedical Research Laboratory (USAARL) at Fort Rucker, Alabama, USA.

Kristin J. Heaton is a Research Psychologist and Deputy Chief of the Military Performance Division at the U.S. Army Research Institute of Environmental Medicine (USARIEM) in Natick, MA, USA.

Richard A. McKinley is the Lead for the Cognitive and Physical Performance Core Research Area within the Airman Bioengineering Division of the U.S. Air Force Research Laboratory's 711th Human Performance Wing in Dayton, OH, USA.

Arcangelo Merla is Associate Professor of Biomedical Physics at the Department of Neurosciences, Imaging and Clinical Sciences, and Director of the Infrared Imaging Lab at the G. d'Annunzio University of Chieti-Pescara, Italy.

John F. Tangney is Director of the Human and Bioengineered Systems Division in the Warfighter Performance Department of the U.S. Office of Naval Research (ONR) in Arlington, VA, USA.

Jan Van Erp is a Principal Scientist at The Netherlands Organization for Applied Scientific Research (TNO), Netherlands, and a Professor of Tangible User Interaction at the University of Twente, Netherlands.

Oshin Vartanian is a Defense Neuroscientist at the Defense Research and Development Canada (DRDC) in Toronto, ON, Canada.

Annika Vergin is an Assistant Section Chief of Future Analysis at the Bundeswehr Office for Defense Planning, Berlin, Germany.

Annalise Whittaker is a Scientist in the Human Systems Group at the Defense Science and Technology Laboratory (DSTL), Porton Down, Salisbury, UK.