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Neuroenhancement in Military Personnel: Conceptual and Methodological Promises and Challenges

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NORTH ATLANTIC TREATY
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RESEARCH AND TECHNOLOGY
ORGANIZATION

AC/323(HFM-311)

www.STO.nato.int

STO TECHNICAL REPORT

STO-TR-HFM-311

Neuroenhancement in Military Personnel: Conceptual and Methodological Promises and Challenges

Final report of Research Task Group HFM-311

Neuroenhancement in Military Personnel: Conceptual and Methodological Promises and Challenges

Executive Summary

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. This final report summarizes technical activities of the NATO Human Factors and Medicine panel activity entitled *Cognitive Neuroenhancement: Techniques and Technology (HFM-311)*, including a review of the state of the art in cognitive neuroenhancement research and development emerging from five participating nations: Canada, Germany, The Netherlands, United Kingdom, and the United States of America. Six neuromodulation techniques are considered, including transcranial magnetic stimulation (TMS), transcranial focused ultrasound stimulation (tFUS), transcranial electrical stimulation (tES), transcutaneous peripheral nerve stimulation (tPNS), photobiomodulation (PBM), 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. Representatives from each participating nation 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 behaviour, 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, cognitive 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

Abstract

Military personnel face harsh conditions that strain their physical and mental well-being, depleting resources necessary for sustained operational performance. Future operations will impose even greater demands on soldiers in austere environments with limited support, and new training and technological approaches are essential. This report highlights the progress in cognitive neuroenhancement research, exploring techniques such as neuromodulation and neurofeedback, and emphasizes the inherent challenges and future directions in the field of cognitive neuroenhancement for selection, training, operations, and recovery.

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List of Acronyms

3D	Three-Dimensional
AC	Alternating Current
ACC	Anterior Cingulate Cortex
AFOSR	Air Force Office of Scientific Research
AI	Artificial Intelligence
APA	American Psychological Association
ARL	Army Research Laboratory
ARO	Army Research Office
ASL	Arterial Spin Labelling
ATP	Adenosine Triphosphate
BCI	Brain-Computer Interface
BIS/BAS	Behavioural Inhibition System/Behavioural Approach System
BMVg	Federal Ministry of Defense
BOLD	Blood Oxygenation Level Dependent
CAF	Canadian Armed Forces
CBRNE	Chemical, Biological, Radiological, Nuclear, and Explosive
CES	Cranial Electrotheraphy Stimulation
CL	Contact Lens
COI	Conflict of Interest
COX	Cytochrome C Oxidase
CPT	Continuous Performance Task
DARPA	Defense Advanced Research Projects Agency
DC	Direct Current
DHEA	Dehydroepiandrosterone
DNA	Deoxyribonucleic acid
DND	Department of National Defence
DoD	Department of Defense
dlPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalography
EMG	Electromyography
FEF	Frontal Eye Fields
FDA	Food & Drug Administration
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near-Infrared Spectroscopy
GABA	Gamma-Aminobutyric Acid
HFM	Human Factors in Medicine
HPA	Hypothalamic-Pituitary-Adrenal
ISE	Ion-selective Electrodes
ISF	Interstitial Fluid
KSAs	Knowledge, Skills, and Abilities
LC	Locus Coeruleus
LIFU	Low-intensity Focused Ultrasound
M1	Primary Motor Cortex
MAUDE	Manufacturer and User Facility Device Experience
MCDC	Multinational Capability Development Campaign

MEG	Magnetoencephalography
MI	Mechanical Index
MoD	Ministry of Defence
MRI	Magnetic Resonance Imaging
NATO	North Atlantic Treaty Organization
NCO	Noncommissioned Officer
NE	Norepinephrine
NF	Neurofeedback
NO	Nitrous Oxide
osc-tDCS	Oscillatory Transcranial Direct Current Stimulation
PANAS	Positive and Negative Affect Scale
PBM	Photobiomodulation
PFC	Prefrontal Cortex
rTMS	Repetitive Transcranial Magnetic Stimulation
RVIP	Rapid Visual Information Processing
S1	Primary Somatosensory Cortex
SA	Situational Awareness
SAM	Sympathetic Adrenal Medulla
SAS	Supervisory Attentional System
SOA	Stimulus Onset Asynchrony
TBI	Traumatic Brain Injury
TBS	Theta Burst Stimulation
tACS	Transcranial Alternating Current Stimulation
taVNS	Transcutaneous Auricular Vagus Nerve Stimulation
tcD	Transcranial Doppler Sonography
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
tFUS	Transcranial Focused Ultrasound Stimulation
tES	Transcranial Electrical Stimulation
TI	Thermal Index
TIC	Thermal Index for Cranial Bone
TNO	Netherlands Organization for Applied Scientific Research
tPNS	Transcutaneous Peripheral Nerve Stimulation
tRNS	Transcranial Random Noise Stimulation
tTNS	Transcutaneous Trigeminal Nerve Stimulation
tVNS	Transcutaneous Vagus Nerve Stimulation
UAV	Unmanned Aerial Vehicle
ubicomp	Ubiquitous Pervasive Computing
UHN	University Health Network
V1	Primary Visual Cortex
WRAIR	Walter Reed Army Institute of Research

Foreword

The following chapters highlight international perspectives on current and emerging neuroenhancement tools and technologies and their prospective use in multinational military settings.

Chapter 1

Brunyé, T. T., Feltman, K. A., Vartanian, O., Beaudoin, M., Wester, B., Hamilton, L., Ohiri, K., Greenwald, H., Heaton, K. J., & Van Erp, J. (2023). Importance of cognitive neuroenhancement for military applications.

Chapter 2

Brunyé, T. T., Heaton, K. J., Vartanian, O., & Van Erp, J. (2023). Current and emerging technologies and research in cognitive neuroenhancement.

Chapter 3

Brunyé, T. T., Heaton, K. J., Feltman, K. A., Vartanian, O., Van Erp, J., Whittaker, A. H., & Beaudoin, M. (2023). Methodological challenges for cognitive neuroenhancement.

Chapter 4

Brunyé, T. T., Vartanian, O., & Feltman, K. A. (2023). Important considerations for cognitive neuroenhancement.

Chapter 5

Beaudoin, M., Wester, B., Hamilton, L., Ohiri, K., & Brunyé, T. T. (2023). Future directions in cognitive neuroenhancement.

Chapter 6

Van Erp, J., Vartanian, O., Heaton, K. J., & Brunyé, T. T. (2023). Summary recommendations for cognitive neuroenhancement research and development.

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Chapter 1 – IMPORTANCE OF COGNITIVE NEUROEHANCEMENT FOR MILITARY APPLICATIONS

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1.1 BACKGROUND

The Cognitive Neuroenhancement: Techniques and Technology activity was organized in 2019 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 intended to report 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 deployment. The activity encompasses techniques, technologies, and/or interventions that target cognitive performance enhancement, readiness/resilience, and accelerate recovery/reset.

The HFM-311 activity group includes defence scientist representation from five NATO member nations: Germany, The Netherlands, United Kingdom, Canada, and the United States of America.

The group convened its first annual in-person member meeting on 9-11 December 2019 in Toronto, Ontario, Canada, hosted by Defence Research and Development Canada – Toronto Research Centre. This meeting included roundtable discussions, national briefings on research and development progress and plans, data collection and analysis demonstrations, information exchange, and collaborative planning.

The group convened its second and third annual member meetings remotely on 9-11 December 2020 and 6-8 April 2021. These meetings included roundtable discussions, national briefings on research and development progress and plans, final report structuring and planning, information exchange, and collaborative research planning.

The group convened its fourth annual member meeting on 6-9 December 2022 in Toronto, Ontario, Canada, hosted by Defence Research and Development Canada – Toronto Research Centre and University of Toronto. This meeting included roundtable discussions, national briefings on research and development progress and plans, final report updates, and briefings from scientists and practitioners at the University Health Network (UHN).

The group convened its final meeting on 30 May to 2 June 2023 in Leiden, the Netherlands, hosted by The Netherlands Organization for Applied Scientific Research (TNO). This meeting included roundtable discussions, national briefings on research and development progress and plans, finishing touches on the final report, and tours of TNO facilities.

This chapter summarizes the strategic imperatives for cognitive neuroenhancement research and development efforts in the context of military applications, the mental processes being targeted and their putative neural substrates, the potential effects of cognitive neuroenhancement on individual and team performance. Finally, the chapter defines the scope of this report, terminology used, and a taxonomy of cognitive neuroenhancement technologies and suitability for application to military training, operations, and recovery.

1.2 DEFINING COGNITIVE NEUROENHANCEMENT

Neuroenhancement involves the application of neuroscience-based techniques and technologies to alter central and/or peripheral nervous system activity and enhance mental function (Clark & Parasuraman, 2014; Farah et al., 2004). 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 (Brunyé et al., 2020). The literature presents a plethora of approaches to achieve both cognitive enhancement and optimization – for example: pharmacological, neuromodulation, neurobiotechnology approaches, cognitive-behavioural approaches (e.g., mindfulness meditation), to name only a few. Common to all forms of modulation approaches, however, is the use of common, typically laboratory-based baseline measurements of cognitive performance which allow various methods to be assessed equally for efficacy. Without baseline measurements, neither cognitive optimization nor enhancement may be assessed.

1.3 MOTIVATING COGNITIVE NEUROENHANCEMENT

Research, development, and engineering in cognitive neuroenhancement are motivated by advances in biotechnology, strategic military imperatives, and competitive adversarial pursuits.

1.3.1 Advances in Biotechnology

"If the 20th century was the century of physics, the 21st century will be the century of biology" (Venter & Cohen, 2004). The biggest innovations of the 21st century are expected to be at the intersection between biology and technology, and are propagated by advancements in materials, fabrication, electronics, sensors, energy storage, and machine learning and artificial intelligence. In recent years, these capabilities have enabled a revolution in biotechnologies that support cognitive and neural enhancement, which has a broad range of applications for training, human performance enhancement, and human integration into intelligent systems. Below we highlight where these enabling capabilities have been key differentiators.

1.3.1.1 Tissue engineering.

Modern tissue engineering is a multidisciplinary endeavour with contributions from both the engineering and life sciences fields. Advances in nanotechnology and nanomaterials-based strategies for neural engineering constructs and interfaces have typically focused on health applications, such as new strategies for preventing and treating neural injury (Kumar et al., 2020; Spearman et al., 2018). In the future, these advances may also enable the use of cognitive neuroenhancement technologies by improving the design of biological tissue-technology interfaces and neuromodulation approaches. Researchers are gaining an increasingly better understanding and command of artificial scaffolds that incorporate appropriate chemical (Heet al., 2020; Ng et al., 2019), biophysical (Lu et al., 2021), and even electrical (Ritzau-Reid et al., 2020) cues to encourage tissue regeneration at the site of injury. New strategies for scaffold formation and tissue models may give researchers more control over tissue architecture and incorporated cues, and someday may guide improved integration of neurotechnology and modulation of neural activity. One technique which allows scientists to control cellular architecture is bioprinting, the 3D layer-by-layer assembly of living cell and biomaterials. Bioprinting allows researchers to more closely mimic natural, three-dimensional extracellular matrices found in the body, enhancing regenerative properties (Aljohani et al., 2018; S.-J. Lee et al., 2018). Bioprinting can also enable the formation of three-dimensional tissue models, useful for mechanistic and translational studies, including drug development (S.-J. Lee et al., 2018). Brain organoids, lab-grown spheroid cellular structure resembling the architecture of the parent organ, are useful for investigating neural development and disease (Mansour et al., 2018). In the future, using tissue engineering approaches may allow researchers to experimentally model functional interactions between specific neuronal subtypes. Tissue engineering advances may enable the development of sophisticated neuromodulation technologies for cognitive neuroenhancement, even in able-bodied individuals.

1.3.1.2 Bioelectronics

The field of bioelectronics bridges abiotic and biotic interfaces, building "read-write" systems that can both report on electronic information from biological systems and deliver electronic signals to biological systems. There have been significant advancements in the development of neural probes and other brain-computer interface (BCI) technologies, including classification of signal features that allow for real-time interpretation of neural activity for both recording and stimulation. An emerging class of bioinspired, flexible bioelectronic systems for chronic neural interfacing has shown exciting potential, boasting high-resolution recordings and long-term biocompatibility and minimal immune response (Khodagholy et al., 2015; Li et al., 2020; McGlynn et al., n.d.; Song et al., 2020). These new neuroelectronic devices provide tools for diagnosis and treatment of neuropsychiatric conditions and new avenues for functional brain computer interfaces (Jastrzebska-Perfect et al., 2020). The field of bioinspired prosthetic interfaces is growing and includes skin-inspired multifunctionality at the prosthetic level using flexible electronics and electronic interfacing between the prosthesis and nervous system using implantable and minimally invasive bioelectronics (Li et al., 2020). An interesting recent development in bioelectronics is the development of so-called morphing electronics, which can adapt to the growth and stretch of nerve tissue *in vivo*, improving biocompatibility and enabling direct nerve interfacing (Liu et al., 2020).

1.3.1.3 Biosensing

Biosensors are analytical devices that use a biological recognition element to sense a target analyte, typically converting to a colorimetric or electronic readout. Of relevance to neural enhancement are recent advancements in biosensors that allow for non-invasive and minimally invasive interrogation of physiological signatures of internal cognitive states; for example, previously underexplored biofluids including sweat, tears, saliva, and interstitial fluid (ISF) (Zhao et al., 2019). New sensing technologies, unique form factors (Currano et al., 2018), and multimodal functions are promising clinical-grade assessments of health status and disease conditions outside of typical hospital settings soon (Mohankumar et al., 2021; Shetti et al., 2020; Tu et al., 2020; Zhao et al., 2019). Similar functionality could be used to monitor physical and emotional state of the Warfighter during training operations (Seshadri et al., 2019a) or in theatre. Additionally, advancements in scalable data infrastructures, compute, and artificial intelligence will play a role in enabling higher rate analyses and assessments to allow for more rapid reporting and targeting. While challenges still need to be overcome before widespread adoption, the field is moving fast and is set to make a large impact.

1.3.1.4 Quantitative Models of Neuroenhancement

Computational neuroscience models use equations and algorithms to simulate aspects of the brain and offer quantitative, falsifiable representations of our beliefs about and understanding of neurophysiology and cognition. Comparing models' predictions with associated empirical data can validate our understanding or demonstrate that the models' underlying assumptions and beliefs need to be re-examined. Models can also reveal questions that can be addressed experimentally or answer questions that are difficult to investigate in the laboratory (Lu et al., 2019).

Most recent models of electrical current propagation through human tissue have relied on finite element models, which approximate complex physical phenomena in a piecewise manner along 3D meshes, to represent how electric fields propagate from the stimulation device or electrodes through biological tissue (see open-source toolkits SimNIBS (Saturnino et al., 2019) and ROAST (Huang et al., 2019). Likewise, models for tFUS have focused on how ultrasonic energy propagates through the skull (Chen et al., 2022; Felix et al., 2022). While early models assumed liquid- or gel-filled spherical heads, models from the past twenty years have used individuals' MRI data to construct personalized geometric representations of grey matter, white matter, bone, skin, cerebrospinal fluid, and air, all of which have different conductive properties. Huang et al. (2017) compared their models' predictions to measurements from cortical and depth electrodes and found that individualized models produced better predictions than an average model. Incorporating MRI data from the neck further improved results, although capturing local differences in bone density and white matter anisotropy did not have significant impacts. Incorporating other aspects like fatty tissue, muscle, vasculature, ocular tissue, and glands could also enhance predictions (Huang et al., 2017; Gomez-Tames et al., 2021).

In addition to variations in cranial structure and composition across individuals, there are multiple sources of uncertainty and noise related to signal propagation that make modelling neuroenhancement effects challenging. Even when the location of the stimulation device is carefully controlled, it is difficult to determine how much current reaches underlying cortical areas, especially since current often spreads laterally and not just perpendicularly into the brain. For tES, the largest electric fields occur between the stimulation electrodes rather than underneath them. Cerebrospinal fluid can transport current to deeper structures (Huang et al., 2017). Local current intensity is often inferred from other measures that do not vary linearly with current (Edwards et al., 2013). Moreover, it is unknown how induced electric fields differentially affect specific neuron types (Weise et al., 2020), but cell geometry makes a difference since electrical stimulation is most effective when a neuron's axis aligns with the axis of the electric field. Therefore, point neuron models, which ignore cell geometry, are insufficient for modelling the effects of electrical stimulation.

Understanding how energy used in neuroenhancement techniques propagates through the brain is important, but what are the mechanisms by which this energy interacts with normal neural functions to influence cognitive processes? While there are hypotheses about how various neuroenhancement techniques work at a coarse level, the current understanding of these mechanisms remains insufficient to explain observed effects on cognitive performance. The next step is to continue efforts to model low-level interactions between propagating energy and neurobiological structures that drive changes within neural populations and at the cellular and sub-cellular scales (Aberra et al., 2020; Shirinpour et al., 2021). These models will require data from further neurophysiological studies that investigate neurostimulation at these scales. Ideally, the models of signal propagation described above could be integrated with biophysically realistic neuron models and computational cognitive models to make predictions about how neurostimulation alters cognitive functions like attention and decision making. The resulting predictions about the mechanisms could be validated in the lab or inform questions that could be addressed experimentally. Candidate cognitive models must include biophysically realistic elements at or below the synaptic level that respond to electrical, ultrasonic, or other relevant stimulation modalities and contain sufficient detail about relevant structural properties (e.g., for measuring alignment with electric fields). Also, the models would need to account for the multiple sources of uncertainty, including the precise location of neurostimulation. The technical challenges of building the necessary integrated framework are significant, but it could test hypotheses about the mechanisms of neuroenhancement, explain the observed benefits for cognitive performance, and provide insights into the long-term effects and other consequences, whether advantageous or adverse, that have not yet become apparent from behavioural studies alone.

1.3.1.6 Supporting Technology

Critical to the development of neurobiotechnology for enhancement and wearable biosensors for long term monitoring of cognitive performance are approaches to improve device form factor, power, and communication. Flexible, next-generation Li-ion batteries provide safe and robust high energy density power for on-body electronics, with inherent form factor flexibility (Logan et al., 2020; Yang et al., 2017). Sweat-activated biocompatible batteries have been developed specifically for epidermal electronic systems (Bandodkar et al., 2020). Alternative methods for on-body energy harvesting are also being developed which can help to power technologies that interface with the body (Mohsen et al., 2021). Communication technologies for secure and efficient data streaming from sensors are critical, including wireless and encapsulated solutions. There are significant challenges, but recent demonstrations highlight key capability development (Currano et al., 2018).

1.3.2 Strategic Imperatives

In Canada, the Department of National Defence (DND) released the “Strong Secure Engaged: Canada’s Defence Policy” document, which acknowledges that improvements to situational awareness and intelligence will increase the security of both Canada and Canadian Armed Forces (CAF) deployed in operations. As such, the CAF is actively exploring methods to enhance cognitive capabilities to support personnel in completing complex tasks that require extended cognitive abilities. The approach aims to improve human cognitive capabilities without being limited to specific means. The primary focus is on achieving the goal of enhancing cognitive abilities and measuring the resulting improvements in terms of task performance, dynamic workload, and memory in real-world scenarios. This approach may incorporate the use of technological tools, such as compact computational devices, ubiquitous pervasive computing (ubicomp), or portable augmented reality systems. These technologies can be applied to address challenges related to improved individual wayfinding, enhanced vision (including expanding the perceivable spectrum), and effective visualization of large databases. The human factors associated with visualizing extensive databases hold particular significance in this context.

In the United States, the Department of Defense (DoD) has several strategic documents that outline the motivation and objectives for research and development on human performance enhancement. One of the key documents is the "Defense Science and Technology Strategy" published by the Office of the Under Secretary of Defense for Research and Engineering. This strategy highlights the importance of human performance optimization and enhancement to ensure military superiority. Additionally, the United States Army has its own strategic documents called the "Army Modernization Strategy," and “People Strategy.” The Modernization Strategy emphasizes the need to invest in research and development efforts focused on enhancing soldier performance; it identifies human performance optimization as a critical capability for maintaining operational effectiveness in future conflicts. The "Army People Strategy" is a comprehensive approach that prioritizes the optimization of its personnel. It focuses on attracting, developing, retaining, and caring for soldiers and civilians in the Army. This strategy links to human performance enhancement through its emphasis on talent management, holistic health and fitness, leader development, and professional military education. By investing in these areas, the Army aims to improve the cognitive, physical, and emotional capabilities of its personnel, ultimately enhancing their overall performance and operational effectiveness. Additionally, the strategy recognizes the importance of diversity, equity, and inclusion in creating an environment that fosters innovation and maximizes the potential of all individuals. Finally, the Warfighter Brain Health Initiative (2022) outlines the U.S. DoD strategy to better address the brain health needs of Service members, their families, line leaders, commanders, and their communities at large. The strategy and action plan addresses brain exposures, to include blast exposures, traumatic brain injury (TBl) and long term or late effects of TBI, with the goal of optimizing brain health and countering TBI.

In Germany, the Federal Ministry of Defence (BMVg) addresses research and development related to human performance enhancement through various strategic documents. The "Capability Profile of the Bundeswehr" outlines the need to enhance soldiers' physical and cognitive capabilities to ensure operational readiness. Furthermore, the "Science and Technology Strategy" of the German Armed Forces highlights the importance of human performance research to support military effectiveness. Furthermore, in 2021, the German Institute for Defence and Strategic Studies led the Multinational Capability Development Campaign (MCDC) which represented a collaboration between Germany and a multinational defence team including Sweden, New Zealand, Germany, France, Great Britain, Finland, Switzerland and the United States. One outcome of this program was a report defining and motivating Human Performance Optimization and Enhancement, which recognizes the need for interdisciplinary and multinational collaboration to analyse ongoing and planned Human Performance

Augmentation programs, ensuring interoperability and preparedness for future conflict scenarios. The project identifies challenges related to common terms of references, optimizing performance, interoperability, isolated programs, and legal/ethical frameworks. Recommendations include adopting common definitions, conducting meta-analyses of existing programs, sharing best practices, establishing a dedicated center of excellence, addressing the impact of human performance augmentation on future warfare, and developing multilateral legal and ethical frameworks.

In The Netherlands, the Ministry of Defence (MoD) emphasizes human performance enhancement in its strategic planning. The "Strategic Research Agenda" (Ministerie van Defensie, 2020) of the MoD focuses on various research areas, including human factors and human performance optimization. This document sets the direction for the MoD's research and development efforts, with an aim to improve the capabilities and performance of military personnel while taking ethical, legal, and societal consideration into account (Ministry of Defense, 2019).

In the United Kingdom, the Ministry of Defence (MoD) focuses on research and development related to human performance enhancement. While there isn't a specific single document that exclusively addresses this topic, various strategic publications highlight the importance of optimizing human capabilities. The "Defence Science and Technology Strategy," published by the MoD, outlines the research priorities, including human factors, human performance, and human-machine interfaces.

These nations include a shared focus on enhancing human performance in the defence sector. In Canada, the Department of National Defence aims to improve cognitive capabilities and task performance through technological tools. The United States emphasizes human performance optimization and enhancement in its defence strategies, with a comprehensive approach in the Army People Strategy. Germany addresses human performance enhancement in its Capability Profile and Science and Technology Strategy, while also recognizing the importance of interdisciplinary and multinational collaboration through the Multinational Capability Development Campaign. The Netherlands prioritizes human performance enhancement in its Strategic Research Agenda, and the United Kingdom highlights human factors and performance optimization in its defence research priorities. These nations share a commitment to improving human capabilities to ensure operational readiness and military effectiveness.

1.4 TARGETED COGNITIVE PROCESSES & NEURAL MECHANISMS

Warfighters must perform numerous job tasks as part of their day-to-day military occupational and training activities. These tasks can vary widely in terms of their complexity, novelty, and difficulty, as can the demands they place on the Warfighter’s physical and cognitive competencies. The conditions under which these jobs are carried out can also contribute to the overall workload demands, such as the need to work quickly in extreme heat or cold or when wearing chemical, biological, radiological, nuclear, and explosive (CBRNE) protective equipment. To be successful, the Warfighter must possess and apply the appropriate cognitive competencies or resources required to meet the demands presented by both task and setting. A wealth of research supports the observation that cognitive abilities are perhaps the most critical individual trait for predicting job-related performance across a wide range of organizational and occupational contexts (Hunter & Schmidt, 1998; Ones et al., 2005). For example, an analysis of occupations within the CAF indicated that cognitive ability is the most important competency identified for the analyzed occupations, topping a list of 21 competencies that included several personality (e.g., conscientiousness), interpersonal (e.g., communication), and organizational (e.g., leadership) factors (Kemp & St-Pierre, 2009). Research suggests approaches aimed at improving cognitive performance in healthy adults can positively influence military-relevant occupational performance (Blacker et al., 2018; Brunyé et al., 2020; Feltman et al., 2020; Fischer et al., 2015; Hamilton et al., 2019; Jensen et al., 2020; Simons et al., 2016; Zanesco et al., 2019). Understanding which cognitive skills and abilities contribute to successful performance of military occupational tasks can further refine targeted cognitive enhancement methods to achieve meaningful and relevant benefits for the Warfighter.

A common method for determining the requisite knowledge, skills, and abilities (KSAs) needed to effectively perform a given job is the task analysis. There are many examples of such analyses in the published and grey literature, with most addressing objectives related to personnel selection (e.g., Damos et al., 2011; Forgues, 2014; Ogle et al., 2015, 2019), occupational assignment (e.g., Foulis et al., 2017), and training applications (e.g., Cannon-Bowers et al., 2013; Knapp, 1994; Tack & Angel, 2005). While many of military job task analyses have focused primarily on observable behaviours, several have been conducted that specifically address the cognitive processes involved in each work task (a cognitive task analysis), often from the perspective subject matter experts. A recent Delphi study reached consensus across dozens of experts asked to identify the most critical mental functions necessary for sustained performance under stress; within the defence sciences application domain, the top five functions were attention, arousal, processing speed, cognitive control, and working memory (Albertella et al., 2022). In this section, we explore the relevant cognitive competencies identified as important for successful job performance across occupational categories, highlighting specific occupational tasks where appropriate.

1.4.1 Sensation and Perception

The interlinked functions of sensation (the process by which information about the external environment and one's internal state is transmitted to the brain via sensory systems) and perception (the process by which information from sensory systems is recognized, organized, and interpreted into meaningful knowledge that can be acted on) form a critical basis upon which higher order cognitive processes operate. Cognitive task analyses of military jobs generally highlight the central role vision plays in the successful execution of many if not most tasks. Among the vision-based functions most often cited in task analyses are visual scan and target selection/discrimination; these have been well studied and described in the literature (for examples, see: Brunyé et al., 2018; Wolfe, 2020).

The ability to conduct a rapid but thorough visual scan of the surrounding environment and accurately select relevant from irrelevant objects or features is key to numerous military job tasks, including but not limited to tactical surveillance, reconnaissance, navigation, marksmanship, manoeuvre, flight operations, assault, and medical triage and treatment. All such activities rely on the ability of the Warfighter to rapidly conduct visual scans of the environment around them and subsequently identify and select objects of interest (targets) from surrounding features (Tack & Angel, 2005; Kelley et al., 2011). Auditory sensing has been cited as central to communications, particularly with respect to receiving and attending to verbal commands and other communications (Burke et al., 2004; Damos et al., 2011; Tack & Angel, 2005). Tactile sensing was highlighted as particularly important for medical triage and treatment job tasks (e.g., Cannon-Bowers et al., 2013), but generally regarded as less important (relative to visual or auditory modalities) for many other job categories. Across domains, the quality and complexity of the information that is sensed and perceived can vary tremendously, thus the ability to rapidly perceive and accurately comprehend the meaning and intent of complex information, often under time pressure, has been identified as an important cognitive capability for many military job tasks, particularly for highly technical jobs such as unmanned aerial vehicle (UAV) operators (Melcher et al., 2019), surgeons (Pugh & DaRosa, 2013), and officers/commanders (Tack & Angel, 2005). Notably, perceptual speed was rated as third out of the ten most important abilities for military aviators across diverse mission types (Miller et al., 1981).

1.4.2 Attention

According to the American Psychological Association (APA), attention is a state in which cognitive resources are focused on certain aspects of the environment rather than on others and the central nervous system is in a state of readiness to respond to stimuli. Because it has been presumed that human beings do not have an infinite capacity to attend to everything—focusing on certain items at the expense of others—much of the research in this field has been devoted to discerning which factors influence attention and to understanding the neural mechanisms that are involved in the selective processing of information. For example, past experience affects perceptual experience (we notice things that have meaning for us), and some activities (e.g., reading) require conscious participation (i.e., voluntary attention). However, attention can also be captured (i.e., directed involuntarily) by qualities of stimuli in the environment, such as intensity, movement, repetition, contrast, and novelty.

A wealth of research has been done to examine the role and vulnerability of vigilant attention in simple tasks (for a review see Langner & Eickhoff, 2013). Currently, there is evidence to suggest that right-lateralized brain networks play a pivotal role in vigilance. A review by Langner and Eickhoff (2013) suggested that right-lateralized regions including the dorsomedial, mid and ventrolateral PFC, anterior insula, parietal cortex, and several sub-cortical areas mediate vigilance. Studies with individuals experiencing damage to right frontal cortical areas have shown these individuals to demonstrate a greater performance decrement over time during sustained attention tasks (e.g., Koski & Petrides, 2001; Rueckert & Grafman, 1996). Moreover, in a review of studies using transcranial Doppler sonography (tcD) during vigilance tasks, it was confirmed that decreases in right-hemisphere blood flow velocity over time occurred that corresponded with behavioural responses consistent with the vigilance decrement (Warm et al., 2008). However, how these networks activate when assessed using different vigilance paradigms has been found to vary, suggesting there is not a clear-cut determination of hemispheric lateralization in all cases. For example, Lawrence et al. (2003) measured fMRI while subjects completed the rapid visual information processing (RVIP) task, which is a validated measure of sustained attention. The results of their analyses found support for frontal, parietal, thalamic, caudate, occipital, and cerebellar activations, similar to what has already been established within the literature, but they also found positive correlations between the left anterior insula, left parietal cortex, and right frontal regions with the number of correct hits on the task. Increased left activation differs from what others have found regarding vigilance being largely right lateralized. This difference could, however, be due to the RVIP requiring not only sustained attention to process the stimuli, but also because it places demands on working memory load. Similarly, Ogg and colleagues (2008) who used the Conners' Continuous Performance Task (CPT) to examine neural correlates associated with task performance also found greater left hemisphere activation for some regions (such as cerebellar), bilateral activation for frontal dorsal regions, and right hemisphere within the ventral frontal and parietal regions. These were attributed to the networks required for task completion, which requires motor control, visual processing, and attentional control. Thus, it may be that right-lateralization occurs with most vigilance paradigms assessed, but when considering the execution of tasks that are more complex, other regions show activation.

1.4.3 Executive Function & Working Memory

The potential to modulate executive functions through various forms of neuromodulation has received the most attention within the literature. Cognitive control, which can be considered a component of executive functions, and summed up as consisting of the processes that are needed to execute goal-directed behaviour, has a long history of research in terms of understanding the mechanisms involved in it. Cognitive control processes mostly take place within the prefrontal cortex (PFC) (Friedman et al., 2022). Several studies using fMRI have linked the cognitive processes that occur during the act of cognitive control (for example, through a Stroop task) to activation within the PFC, dorsolateral PFC and anterior cingulate cortex (ACC) (for a review, please see Friedman et al., 2022). Further, it has been shown that the PFC if functionally connected to most of the cortical and subcortical parts of the brain, thus connecting it with various neural networks and enabling the incorporation of different functional domains, such as visual and auditory domains (Friedman et al., 2022). In this sense, the PFC can be thought of as the meeting grounds for many of the functions that occur within the brain that are needed to execute various tasks.

Working memory serves to actively maintain and manipulate information over short periods of time in support of complex cognitive activities, such as reasoning, comprehension, and problem solving (Baddeley, 1992; Miyake & Shah, 1999). Together, these processes support numerous aspects of Warfighter job performance across most occupational specialties. Sustained and divided attention were identified as very important for rotary wing pilots (Houston & Bruskiewics, 2006). Working memory plays a pervasive role in daily life and is a critical process underlying performance on planning, reasoning and problem solving, and decision-making tasks (Davidson & Sternberg, 2003; Gilhooly, 2004; Hinson et al., 2003; Kyllonen & Christal, 1990). It has also been a topic of interest among cognitive neuroscientists interested in mapping working memory processes to brain regions and networks, which has found strong evidence that the lateral PFC is involved in the temporary maintenance of task-relevant information, and that the distribution of brain activity across widespread networks is dependent on many task-related parameters such as the sensory modality being used (e.g., visual, auditory), the nature of stimuli (e.g., verbal, spatial, motor, faces) being maintained or manipulated, and whether the information is retrospective or prospective (D'Esposito, 2007). In general, the PFC appears to be a critical node in a distributed working memory network that coordinates the involvement of other brain regions more specialized in specific functions (e.g., sensory, representational, and action-related) (Postle, 2006).

1.4.4 Learning & Long-term Memory

Learning and memory are fundamental cognitive functions that play a crucial role in human cognition (Anderson, 2000; Thompson, 1986). Learning refers to the process of acquiring new knowledge, skills, or behaviours through experience, instruction, or observation. It involves the encoding, storage, and retrieval of information. Memory, on the other hand, refers to the ability to retain and recall information that has been previously learned or experienced. It encompasses various forms such as short-term memory, long-term memory, and working memory. Memory involves the encoding of information (verbal and nonverbal) that has been acquired through experience and learning, the retention of that information for future use, and the ability retrieve that information at a later point in time. Military job tasks require both short-term memory storage for processes and procedures relevant to a specific mission or task, and longer-term memory storage that forms the basis of experience and expertise. The need to store information relevant for future tasks was reported as relevant to military jobs at both infantry and command levels in a cognitive task analysis of Canadian Armed Forces jobs (Tack & Angel, 2005), and memory was identified as important to overall job performance in 29 out of 91 Canadian Armed Forces jobs (Kemp & St-Pierre, 2009). Houston & Bruskiewics (2006) cited memory (particularly long- term memory) as among the most important capabilities of rotary wing pilots.

These cognitive functions hold particular significance for Warfighters in military operations. The ability to learn quickly and efficiently is essential for acquiring new tactics, strategies, and procedures, allowing Warfighters to adapt and respond effectively to changing and complex environments on the battlefield. Additionally, memory plays a vital role in retaining critical information, such as mission objectives, operational procedures, and intelligence data. The capacity to recall and apply this knowledge accurately in high-pressure situations is crucial for decision-making, problem-solving, and overall mission success. Furthermore, learning and memory also contribute to skill development, enabling Warfighters to master complex tasks, weapon systems, and communication protocols. By leveraging these cognitive functions, Warfighters can enhance situational awareness, anticipate threats, and execute missions with precision and efficiency, ultimately ensuring the safety and success of military operations.

1.4.5 Language & Communication

Language can be defined as a system of communication that involves the use of words, symbols, and grammar to convey meaning. It enables individuals to express their thoughts, share information, and engage in social interactions. Communication, on the other hand, encompasses the exchange of messages, ideas, or emotions between individuals through various channels, such as verbal, non-verbal, written, or visual (Beattie & Ellis, 2017; Miller, 1951).

In the context of Warfighters, language and communication play a critical role in facilitating effective command, coordination, and collaboration among military personnel (van Dijk & Soeters, 2008). Clear and precise communication is essential for conveying orders, sharing critical information, and maintaining situational awareness on the battlefield. Warfighters need to understand and interpret instructions, engage in effective dialogue with their team members, and transmit accurate reports and updates. Language and communication skills are vital for establishing rapport, building trust, and fostering cooperation within military units. Furthermore, effective communication can enhance decision-making, mitigate misunderstandings, and reduce errors or misinterpretations that could have severe consequences in combat situations. Overall, strong language and communication abilities are essential for ensuring efficient and cohesive operations, promoting unity among Warfighters, and ultimately contributing to mission success and the safety of personnel.

Finally, the ability to communicate, orally and through writing and gestures, is central to mission success as it provides the means through which information central to all aspects of mission planning and execution is disseminated (Burke et al., 2004; Damos et al., 2011; Tack & Angel, 2005). Expressive cognitive functions primarily include language (fluency, grammar, and syntax), drawing and writing, physical gestures and facial expressions.

1.4.6 Motor & Procedural Function

Psychomotor function refers to movements or motor outputs that emanate from mental activity, often expressed in terms of manual dexterity, coordination, and reaction time. From a cognitive perspective, task analyses have generally rated psychomotor-related military job demands as less important than other cognitive functions (Tack & Angel, 2005). Even so, psychomotor skills were identified as important for the performance of 34 out of 91 military jobs in one large task analysis (Kemp & St-Pierre, 2009). Moreover, Agee and colleagues (2009) reported that psychomotor abilities including rate control, choice reaction time, hand/eye coordination, finger dexterity, multi-limb coordination, and arm-hand steadiness as moderately to highly relevant for U.S. Air Force pilot. Moreover, writing orders, loading ammunition, manipulating the controls of a vehicle (land, sea, or air), navigating difficult terrain, firing a weapon, repairing an engine, or rendering medical care to a patient are all military job tasks that rely on the intricate coordination of central and peripheral motor system function with cognitive control processes (Cannon-Bowers et al., 2013; Tack & Angel, 2005).

Motor and procedural skill acquisition refers to the process of acquiring new abilities to perform novel sequences of skilled behaviours to accomplish a goal, from typing on a keyboard to riding a bike. Acquiring a new skill relies upon experience-dependent neuroplasticity in the brain, often tied to practice and consolidation (Karni et al., 1998; Robertson et al., 2004), which can occur over the course of hours, days, or weeks (Korman et al., 2003). Neuroplastic changes associated with motor skill acquisition are often considered the locus of the primary motor cortex (Kami et al., 1995; Karni et al., 1998; Sanes & Donoghue, 2000). In addition to the motor cortex, the cerebellum has received attention due to its potential involvement in the initiation of limb movements and the improvement of motor skills (Gilbert & Thach, 1977; Houk et al., 1996; Kitazawa et al., 1998; Thach, 1996).

1.4.7 Other Cognitive Functions

In addition to sensory and perceptual processes, cognition includes a broad range of functions aimed at manipulating knowledge (thinking), retaining knowledge (learning and memory), and expressing knowledge and experience (verbal, gestural, and facial communications). These core functions are supported by executive functions, attention, and working memory. Executive functions sub-serve volitional, goal-directed behaviours and adaptive response to novel, ambiguous, or complex stimuli or situations (e.g., strategic planning, reasoning, inhibitory control; see Lezak et al., 2012, Hughes, 2013). Executive functions that have been identified through task analysis as important to military job task performance include reasoning and judgment, problem solving, decision making, planning, ordering, organizing, concept formation, and abstracting across verbal, spatial, and motor modalities (Burke et al., 2004; Tack & Angel, 2005; Kemp & St-Pierre, 2009). Military job tasks relying on these specific cognitive functions include planning and laying out defensive/assault positions, developing a plan of attack and coordinating assault, navigation/wayfinding, to name a few. In a cognitive task analysis of 91 Canadian Forces officer and non-commissioned officer jobs, 56 jobs were identified as requiring good judgment, 53 required analytic/thinking skills, 34 required decision making, 29 required problem solving, and 18 required rapid information processing speed (Kemp & St-Pierre, 2009). Houston and Bruskiewics (2006) cited judgement, decision making and problem solving as the third most important capability (these were categorized together for the purpose of the analysis) of rotary wing pilots.

Visual search refers to the process of finding a visual target among distractors and is typically assumed to involve interactions between pre-attentive processing and focal attention (Chan & Hayward, 2013; Eckstein, 2011; Wolfe, 2010). Visual search is extremely common in applied and daily tasks, such as searching for a weapon in luggage, finding lung nodules on a radiograph, identifying suspects in a crowd, or simply finding a matching pair of socks (Eckstein, 2011). It also recruits a wide range of brain regions including ventral and dorsal regions of the prefrontal cortex (and frontal eye fields [FEF]) (Anderson et al., 2007), multiple areas of the parietal cortex (Donner et al., 2000) and the occipital cortex (Nobre et al., 2003).

Situation awareness (SA), a critical element of military job performance, relies heavily on both attention and working memory. SA involves the perception and comprehension of one’s environment and its features, their meaning and inter-relatedness and their possible future status. Identification of troop locations and status, detection of current and future threats and hazards, navigation and manoeuvre, and awareness of resource needs for mission support are all reliant on accurate SA. In one task analysis, SA was identified as an important capability for performance of 36 out of 91 Canadian Armed Forces officer and non-commissioned officer (NCO) jobs (Kemp & St-Pierre, 2009). SA was identified as the most important capability for rotary wing pilots (Houston & Bruskiewics, 2006) and fighter pilots (Carretta et al., 1993), with working memory identified as only slightly less important (Houston & Bruskiewics, 2006). Demands on attention resources can adversely impact SA. Tack and Angel (2005) reported that attention demands were rated as high across job tasks by both officers and NCOs, particularly within the visual attention domain. In the same study, auditory attentional demands were rated as being higher for infantry than for those in command positions, perhaps due to infantry tasks related to surveillance and the heavier burden of communications both vertically and laterally. Overall, the authors noted that inaccurate situation awareness information contributed to degraded performance on tasks involving control of fire and development of accurate plans, diminished awareness of friendly force status and elevated the risk of fratricide (Tack & Angel, 2005).

Situational awareness plays a critical role in Warfighter function as it enables individuals to perceive and understand the operational environment in which they operate. According to Endsley's model (Endsley, 1995; Endsley & Garland, 2000a,b), situational awareness consists of three levels: perception, comprehension, and projection. Perception involves actively gathering information from the environment through sensory inputs.

Comprehension involves processing and understanding the collected information to form a coherent mental representation of the situation. Projection involves using that understanding to anticipate future events and make informed decisions. For Warfighters, situational awareness is vital as it allows them to assess the current situation, identify potential threats, and make timely and effective decisions. It helps in maintaining a clear understanding of the mission objectives, the terrain, the enemy's capabilities, and the overall situational context. By continuously monitoring and updating their situational awareness, Warfighters can adapt to dynamic and unpredictable situations, anticipate changes, and take appropriate actions.

Ensuring high levels of situational awareness requires training, experience, effective communication, and access to relevant information and intelligence. It also involves managing cognitive load, as information overload or inadequate information can hinder accurate perception and comprehension. Ultimately, situational awareness serves as a foundation for effective decision-making, risk management, and mission accomplishment in military operations.

Finally, higher-order cognitive functions include processes such as problem solving, reasoning, planning, creativity, and judgment and decision making, among others. A defining feature of higher-order cognitive functions is that they represent a hierarchic system, which means "a system that is composed of interrelated sub-systems, each of the latter being, in turn, hierarchic in structure until we reach some lowest level of elementary subsystem" (Simon, 1962). Analogously, higher-order cognitive functions also tend to be componential in structure, meaning that they rely on the contribution and interplay of various components—in this case processes—that are individually necessary and jointly sufficient to support it (see Sternberg, 1980). By extension, evidence regarding the neural bases of higher-order cognitive functions has also revealed that the brain systems that support them reflect both hierarchic and componential features. For example, the components (i.e., cognitive processes) that support creativity include attention, memory, and executive functions, among others. In turn, the neural structures that underpin each component (e.g., PFC for executive functions) reside hierarchically within large-scale neural networks (e.g., executive control network that regulates cognitive control). A similar distributed neural system that includes the contribution of many components has been shown to be true for other higher-order cognitive functions such as reasoning and judgment and decision making (Goel, 2007; Sanfey & Chang, 2008). One can think of higher-order cognitive functions as those that draw on other relatively low-level cognitive functions and processes for their instantiation. Critically, many aspects of performance in real-world (and military) settings draw heavily on higher-order cognitive functions, such as planning operations, solving problems, as well as tactical and strategic decisions, among others.

1.5 DEFINING SCOPE

The scope of this report is limited to a specific population comprising healthy and neurotypical participants who fall within the military-aged range (e.g., 18-65 years). The focus of the report is on examining performance in the laboratory and/or field on military-relevant mental tasks across various training and operational domains, including aviation, dismounted, and multidomain operations. Furthermore, we also restrict this report to non-invasive methods to alter physiology, biochemistry, and mental performance; thus, we do not include implantable or otherwise invasive devices, and do not include coverage of physical performance. Finally, we restrict this report largely to technological interventions and intentionally exclude coverage of nutritional, nutraceutical, and/or pharmacological supplementation methods. By studying this specific population, these interventions, and tasks directly applicable to military scenarios, the report aims to provide insights and recommendations that are most relevant to the needs and requirements of NATO military training and operations.

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Chapter 2 – CURRENT AND EMERGING TECHNOLOGIES AND RESEARCH IN COGNITIVE NEUROENHANCEMENT

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2.1 BACKGROUND

This chapter summarizes current and emerging technologies and research in cognitive neuroenhancement identified and discussed by the group. We explore the field of neuromodulation techniques, which involve the introduction of external energy into the central or peripheral nervous system to alter neural activity and influence behavior and affect. Various methods are employed to achieve neuromodulation, including the application of magnetic, electrical, ultrasonic, and infrared energy to the nervous system. These techniques aim to directly or indirectly modulate neuronal membrane potential and firing rates, leading to neuroplastic changes in the brain and alterations of military-relevant behavior such as learning, skill acquisition, memory, threat detection, situational awareness, and decision making. While each neuromodulation technique has been traditionally studied in isolation, recent reviews suggest the utility of examining converging evidence across multiple neuroenhancement modalities. This chapter focuses on two broad categories of neuroenhancement: neuromodulation and neurofeedback.

2.2 NEUROMODULATION TECHNIQUES

Neuromodulation involves introducing exogenous energy into the central or peripheral nervous system to alter nervous system activity, neurotransmitter and hormonal activity, with the intention to influence affect and behaviour. Many neuromodulation techniques exist, including the introduction of magnetic, electrical, and ultrasonic energy into the central and/or peripheral nervous system. In most cases, the idea is to alter neuronal membrane potential or firing rates and induce neuroplastic changes in the brain (Kricheldorff et al., 2022). While many of these techniques are considered in isolation, recent reviews suggest utility in summarizing converging evidence across neuroenhancement modalities (Byczynski & Vanneste, 2023).

2.2.1 Transcranial Magnetic Stimulation

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 (Klomjai et al., 2015). There are three primary approaches to TMS administration: conventional single-pulse TMS, repetitive TMS (rTMS), and deep TMS. With single-pulse TMS, the system's magnetic coils produce an electromagnetic pulse by switching between positive and negative polarity; this technique is used to produce highly transient modulation of neuronal membrane potentials and initiate action potentials in underlying cortical tissue (Farzan, 2014).

With rTMS, the system produces an electromagnetic pulse that rapidly changes polarity and creates relatively strong and long-lasting electromagnetic induction (Klomjai et al., 2015). In general, low frequency rTMS (≤ 1 Hz) tends to induce inhibitory effects, and relatively high frequency rTMS (e.g., 5-25 Hz) tends to produce excitatory effects. One popular rTMS technique is theta burst stimulation (TBS), which is a form of high frequency rTMS based on the brain's natural theta rhythms arising from the hippocampus, producing both inhibitory and excitatory effects depending upon frequency, intensity, and duration of stimulation parameters (Huang et al., 2005).

Deep brain TMS couples the principles of rTMS with specially designed magnetic coils, such as the H-coil, which can maximize the depth (e.g., 3-6 cm) of the electric field generated in the brain through the summation of multiple magnetic fields (Roth et al., 2007). This contrasts the relatively superficial depth of traditional TMS and rTMS coils, which is typically about 2-3 cm (Deng et al., 2014). Deep brain TMS has been used to target relatively medial regions of the brain, including the anterior cingulate, medial prefrontal, medial sections of the M1 motor cortex, and inferior parietal cortices.

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 (Luber & Lisanby, 2014). Furthermore, the ability to target relatively medial brain regions critically involved in a multitude of cognitive processes, such as the medial PFC, 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," (Luber & Lisanby, 2014). 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 (Dräger et al., 2004). For example, rTMS targeting cortical regions both involved (primary visual cortex, left extrastriate cortex, right angular gyrus) and unrelated (vertex) to visual motion discrimination can induce response time advantages (Campana et al., 2002). 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 (Boyd & Linsdell, 2009). Similarly, online excitatory rTMS targeting the parietal cortex can reduce response times during a spatial working memory task (Yamanaka et al., 2010). In both studies, the authors directly targeted brain regions with demonstrated involvement in the outcome tasks. In a review of effects of TMS targeting the somatosensory cortex, scientists suggest that tactile perception, proprioception, and pain perception can be both disrupted and enhanced via TMS (Tang et al., 2023). In a review of neuromodulation effects on decision making, Levasseur-Moreau and Fecteau (2012) suggest that rTMS can improve certain aspects of decision making, particularly in the context of emotional and social decisions. In more examples of higher order cognition, research suggests that TMS applied to the primary visual cortex (V1) can reduce error rates during a reasoning task (Hamburger et al., 2018), and when applied to the left inferior frontal gyrus it can increase originality during a creative idea generation task (Kleinmintz et al., 2018).

Addition-by-subtraction (Luber & Lisanby, 2014), also termed enhancement through diminishment (Earp et al., 2014), 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, the freeing up of metabolic resources for a critical node (Brem et al., 2014), or degrading automatic processes that are not essential to learning or task performance (Oliveri et al., 2010; Walsh et al., 1998). Nearly half of the identified TMS studies showing cognitive enhancement used the addition-by-subtraction approach. For example, offline rTMS targeting the right dorsal posterior parietal cortex enhanced spatial orienting in the right visual field, suggesting a reduction of interhemispheric inhibition (Thut, et al., 2005). Another study showed that disrupting the right parietal cortex with rTMS reduces attentional capture during a visual search task, suggesting that disrupting an automatic attention-capturing effect of salient singletons can reduce their distracting effect on task performance (Hodsoll et al., 2009).

Thus, there is evidence that TMS can induce cognitive performance enhancement through at least three mechanisms, lending support for TMS in military applications. Beyond that comprehensive review, there is also evidence that TMS (specifically rTMS) can modulate certain aspects of language comprehension; for example, rTMS targeting the left primary motor cortex (M1) can facilitate lexical decision speed with abstract words (Vukovic et al., 2017). 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 manoeuvring, 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 (Kobayashi, 2010; Kobayashi et al., 2004; Kobayashi et al., 2009). In these studies, participants learned a simple motor skill involving the learning and application of a defined sequence of hand movements; rTMS targeted M1 of the hemisphere contralateral or ipsilateral to the hand movement. In most cases, contralateral stimulation interfered with motor skill learning, whereas ipsilateral stimulation facilitated motor sequence execution time and learning. 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 (Gilbert et al. 2004).

A considerable amount of international defence science research has used TMS for clinical and therapeutic purposes, or for basic mechanistic research purposes. However, to our knowledge the defence science community has done limited research exploring TMS for enhancing cognitive performance with military-relevant tasks or contexts. In one such study funded by the U.S. Air Force Office of Scientific Research (AFOSR), TMS was applied to the primary motor cortex, which interfered with response latencies on a mental rotation test involving the mental rotation of hand, but not foot, depictions (Ganis et al., 2000).

Table 1: Approaches, Efficacy, Safety & Maturity of TMS

Transcranial Magnetic Stimulation (TMS)

Approach	Time-varying magnetic fields generate a powerful electrical field in the brain through the process of electromagnetic induction, resulting in suprathreshold modulation of neuronal activity.
Efficacy	Demonstrated efficacy for improving cognitive performance in healthy adults, particularly in domains of attention, learning and memory, and perceptual and motor processes; effects are transient.
Safety	Relatively safe with few side effects; rare serious side effects (headache, seizure, hearing loss).
Maturity	Approach is mature but is generally not robust to austere environments.

2.2.2 Transcranial Electrical Stimulation

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).

With tDCS, a DC electric charge, typically at 2.0mA intensity or less, is passed between an array of two or more electrodes positioned on the surface of the scalp. Electrodes are typically arranged in a bipolar configuration with a single anode and cathode, but sometimes multi-electrode montages are used with two or more anodes or cathodes arranged in a manner designed to increase current density at a focal target (i.e., high-definition stimulation). The tDCS technique is used to induce neuronal membrane depolarization (excitatory) or hyperpolarization (inhibitory) and facilitate the subsequent initiation of action potentials in underlying cortical tissue (Bestmann et al., 2015; Medeiros et al., 2012; Nitsche et al., 2008).

With tACS, an alternating current (AC) electric charge is passed between an array of two or more electrodes, very similarly to tDCS. Unlike tDCS, however, tACS can be administered within a specific resonance frequency that can synchronize or desynchronize ongoing brain oscillatory activity. When tACS is applied within the range of signals typically measured with electroencephalography (EEG), it can be used to entrain or synchronize ongoing neuronal network activity (Antal & Paulus, 2013). For example, parietal stimulation at 10Hz (alpha-band) can increase alpha power, synchronize oscillatory activity measured using EEG, and alter behavioural task outcomes on a visual oddball task (Helfrich et al., 2014).

With tRNS, an alternating current (AC) electric charge is used similarly to tACS, except multiple frequency bands are combined during stimulation, creating the potential to disrupt or desynchronize ongoing brain oscillatory activity. For example, a researcher may be able to entrain multiple variable-frequency oscillations simultaneously, disrupting normal brain rhythms (Terney et al., 2008).

With osc-tDCS, an oscillatory tACS waveform is coupled with a DC offset. This technique was developed to simultaneously synchronize rhythmic activity and alter excitability level (Mizrak et al., 2018).

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 behavioural outcomes (Antal & Paulus, 2013; Dedoncker et al., 2016; Paulus, 2011; Saturnino et al., 2015; Woods et al., 2016).

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 (Kadosh, 2013; Santarnecchi et al., 2015). While tES is thought to primarily modulate relatively superficial cortical layers (Kuo et al., 2013; Nitsche et al., 2008), 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 (Power et al., 2011). 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 behavioural, effects.

Several reviews have been published (Chang, 2022; Kadosh 2013, 2014; Levasseur-Moreau & Fecteau, 2012; Santarnecchi et al., 2015; Senkowski et al., 2022) 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. Several studies using a double-blind, sham-controlled design with random assignment have shown improved cognitive function following tES. For example, a double-blind study with 120 participants showed that anodal tDCS targeting the left or right dorsolateral prefrontal cortex (dlPFC) can enhance adaptive cognitive control relative to sham or motor cortex stimulation (Gbadeyan et al., 2016). Other studies suggest that anodal tDCS targeting the dlPFC can also enhance cognitive control during emotion regulation (Feeser et al., 2014), anodal tDCS targeting the medial PFC can enhance theory of mind in females (Adenzato et al., 2017), anodal tDCS targeting the left primary motor cortex (M1) can enhance recall of action sentences (Vitale et al., 2021), anodal tDCS targeting the right posterior parietal cortex can improve spatial reasoning (Wertheim et al., 2020), anodal tACS over the visual cortex can improve visual perceptual learning (He et al., 2022), tRNS can improve aspects of visual perception and perceptual learning (He et al., 2022; van der Groen et al., 2022), tACS can induce small-to-medium effect sizes when assessing working memory and long-term memory performance (Booth et al., 2022), tACS can improve motor learning (Takeuchi & Izumi, 2021), and anodal tDCS targeting the left inferior frontal gyrus can improve comprehension of simple and complex language (Giustolisi et al., 2018).

The effects of tES on working memory performance have engendered some debate in the scientific literature, with some meta-analyses suggesting improvement of working memory (in accuracy or response times) with anodal tDCS targeting the left or right dlPFC (Brunoni & Vanderhasselt, 2014; Dedoncker et al., 2016; Hill et al., 2016; Mancuso et al., 2016), and another meta-analysis suggesting no evidence for improvement (Horvath et al., 2015). Studies also suggest that anodal and cathodal tDCS over the left FEF can improve target detection during a visual search task (Nelson et al., 2015), that cathodal stimulation of the right posterior parietal cortex (but not FEF) can reduce the benefits of practice in a visual search task (Ball et al., 2013), and that anodal stimulation of the right inferior frontal or posterior parietal cortex can enhance performance on a task involving searching for threats in complex scenes (Callan et al., 2016; Falcone et al., 2012). Studies using tDCS to influence motor skill acquisition variably target the primary motor cortex and cerebellum. Reviews and meta-analyses suggest that anodal tDCS targeting the primary motor cortex can improve motor learning and motor function (Reis & Fritsch, 2011), and both anodal and cathodal tDCS targeting the cerebellum can accelerate motor learning, motor adaptation, and procedural learning (Oldrati & Schutter, 2018). A recent review by He et al. (2022) evaluated the likelihood of enhancing vision perception through the combination of TES and visual perceptual training. In their review, they highlight the plasticity of the visual cortex with support from multiple studies demonstrating improvements through training on a variety of visual skills in healthy adults.

Second, meta-analytic approaches to understanding tES effects on cognitive performance, such as vigilance, working memory, or executive functions, find mixed results (Chhatbar and Feng, 2015; Dedoncker et al. 2016; Hill et al., 2016; Horvath, Forte, & Carter 2015a, 2015b; Mancuso et al., 2016; Medina & Cason, 2017). Specifically, whereas some meta-analyses find significant support for positive effects of tES on cognitive functions, others find no strong evidence for positive or negative effects. There are likely at least four issues why this is the case: 1) varied meta-analytic procedures, including criteria for including versus excluding published studies from the analysis, 2) many published studies have low statistical power due to small sample sizes, 3) varied study designs and populations, and 4) there is likely a strong publication bias wherein null or negative findings are not published as often as positive findings.

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, the number and duration of sessions, and online versus offline stimulation (Jacobson et al., 2012; Steinberg et al., 2019; Senkowski et al., 2022; Tremblay et al., 2014). Variation in one or more of these parameters can lead to different, if not paradoxical, effects, such as non-linear effects of stimulation intensity (Batsikadze et al., 2013), or altered electric field orientations and polarity reversals due to electrode placement and individual differences in neuroanatomy (Dmochowski et al., 2012; Miranda et al., 2013). In another example, Weinberger and colleagues (2017) demonstrated that alterations of stimulation site, polarity, and the nature of outcome tasks can modulate whether tDCS alters certain aspects of creative cognition.

Fourth, the research community lacks a generally accepted mechanistic theory to account for tES effects on brain and behaviour. Many theories have been proposed to detail the molecular, cellular, and electrophysiological effects of tES, and how they might link to improvement in behavioural function. Example theories include sliding scale models (e.g., zero-sum, excitation-inhibition balance, activity-selectivity), stochastic resonance models, and input specificity models (Bestmann et al., 2015). Each model is only able to account for a small portion of extant tES research findings, pointing to a need for more comprehensive mechanistic understandings through experimentation and computational modelling. Interestingly, research shows that only about 25% of electric currents applied at the scalp reach cortical tissue (i.e., are not attenuated by skull and tissue), and that the intensity of tES currents required to reliably modulate neuronal activity may be higher than previously assumed (Voroslakos et al., 2018).

Fifth, combining tES with other enhancement interventions, such as pharmaceuticals, exercise and cognitive training, is an exciting yet under-researched topic. The studies that have examined interactive effects of multiple enhancement approaches suggest promising results; for example, one study showed additive and interactive effects of combining brain stimulation with physical exercise and cognitive training interventions (Ward et al., 2017).

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 behaviour, and at worse it could significantly degrade performance (Berryhill et al., 2010; Brunyé et al., 2018; Matsushita et al., 2015; Sellers et al., 2015; Tang & Hammond, 2013). For example, cathodal tDCS targeting the right inferior parietal cortex can impair working memory (Berryhill et al., 2010), anodal tDCS targeting the left dlPFC can impair long-term verbal memory (Brunyé et al., 2018), and anodal tDCS targeting the right auditory cortex can impair auditory pitch learning (Matsushita et al., 2015). Any implementation of tES in non-research contexts will necessitate a careful understanding and predictive modelling of individual, task, and contextual parameters associated with performance outcomes. For example, research has demonstrated that fixed tES stimulation intensities inevitably lead to subtherapeutic or supratherapeutic doses across individuals (Caulfield et al., 2020).

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 (Antal et al., 2017). 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 (Wexler 2016, 2018; Wexler & Reiner, 2019).

Fourth, no formal clinical certifications exist for safely and reliably preparing and administering tES protocols. This introduces 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 (Antal et al., 2017). This may be exacerbated by application of tES in military settings with sparse medical support and oversight.

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 (Boudewyn et al., 2019; Brunyé et al., 2014; Brunyé 2018, 2021; Brunyé et al., 2018a,b; Brunyé, 2020; Brunyé, Brou, et al., 2020; Kaur et al., 2020; McIntire et al., 2014; McKinley et al., 2013; Mizrak et al., 2018; Nelson et al. 2014, 2015, 2016; Parasuraman & McKinley, 2014).

Table 2: Approaches, Efficacy, Safety & Maturity of TES

Transcranial Electrical Stimulation (TES)	
Approach	Direct or alternating current is used to create diffuse electrical fields on the brain, resulting in subthreshold modulation of neuronal membrane potentials.
Efficacy	Modest evidence supporting cognitive improvement across multiple domains in healthy adults; largely small, inconsistent effects across studies.
Safety	Long term safety is generally unknown; acute applications have few noted side effects.
Maturity	Approach is mature; newer devices are commercially available; no formal clinical certifications exist currently.

2.2.3 Transcranial Focused Ultrasound Stimulation

Transcranial focused ultrasound stimulation (tFUS) uses a pressure wave of ultrasonic frequencies to induce a non-invasive yet highly localized (millimetre-level) stimulation of underlying tissue, resulting in suprathreshold neuromodulatory effects (Kubanek, 2018). 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 (Fry et al., 1958). Since that time, the influence of tFUS on neuronal activity has been investigated in several animal models, including rats, rabbits, and monkeys (Folloni et al., 2019; Krishna et al., 2018).

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 (Legon et al., 2014), directly evoke sensory responses on the fingers and hand (Lee et al., 2015), and alter sensory evoked potentials (Mueller et al., 2014). 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 (Lee et al., 2016). 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 (Legon et al., 2018). While potentially not relevant for healthy, neurotypical populations, one study showed improved language comprehension following tFUS targeting the thalamus in a patient with traumatic brain injury (Monti et al., 2016). In recent reviews of tFUS applications to humans and animals, authors suggest advantages relative to other neuromodulation approaches in terms of spatial selectivity and the ability to excite and inhibit both superficial and medial cortical (and perhaps subcortical) targets (Kim et al., 2021).

Qualitative assessments of tFUS tolerability and adverse effects in humans show symptom frequency and severity (e.g., neck pain, sleepiness, muscle spasms, anxiety) similar to those seen with other forms of non-invasive brain stimulation such as tES (Legon et al., 2018; Legon et al., 2020). Also similar to other forms of brain stimulation, the precise mechanisms by which tFUS induces effects of brain and behaviour are relatively unknown. One proposal suggests that ultrasound can induce mechanical effects on ion channels and thereby modulate neuronal activity (Tyler, 2012), whereas others propose that ultrasonic pressures can induce swelling of astrocytes and membrane depolarization (Jordão et al., 2013).

tFUS has a relatively unknown safety profile. The United States Food and Drug Administration publishes safety guidelines for ultrasound imaging systems, indicating a maximum sonication intensity of 720 mW/cm2 and maximum mechanical index (MI) for soft tissue sonication of 1.9. Below these intensities, ultrasound has a proven safety record when used for diagnostic imaging in medicine (Miller et al., 2012). Above these intensities, however, ultrasound carries substantial risk of mechanical and thermal tissue damage. These effects may be amplified by the relatively focal application of ultrasound with tFUS, increasing total energy relative to the scanning application used with diagnostic ultrasound (Pasquinelli et al., 2019).

Two common mechanical effects of ultrasound are cavitation and radiation pressure. Cavitation occurs when gas bubbles are created, or existing bubbles expand or contract, as acoustic energy induces pressure variation in tissue. Violent gas bubble collapses can occur, possibly damaging tissue. Low-level radiation stress always occurs as the acoustic wave propagates through tissue and fluid, approximating about 68µg per mW of acoustic intensity. Both cavitation and radiation stress can cause significant stress and temperature increases on underlying tissue, which has been relatively well-defined on various biological materials including bone, lung, and intestine (Fowlkes, 2012). In one study, authors found mechanical alterations to migrating neurons in fetal mouse brains can occur after 30 minutes of 330 mW/cm2 sonication (Ang et al., 2006). Thermal effects may also occur with tFUS application; one study showed temperature increases up to 3˚C in the rat cortex with 5 minutes of 200kHz stimulation at 4.5W/cm2, which is above FDA guidelines (Gulick et al., 2017). Most studies examining tFUS in animal models have noted minimal or no evidence of neuronal damage or death, bleeding, alteration of blood-brain barrier permeability, or undesirable changes to animal behaviour (Pasquinelli et al., 2019).

Relatively few studies have examined the safety of focused ultrasound administered to the human cerebral cortex. Existing studies in this area tend to use interview procedures following stimulation to probe for discomfort or changes in mental or physical status; these studies find little to no evidence of noticeable changes in these measures (Lee et al., 2015, 2016). Results from follow-up anatomical MRI scans show similar results (Legon et al., 2018), and when mild to moderate symptoms do occur, they tend to be positively correlated with the intensity of tFUS administered (Legon et al., 2020). A very recent review suggests that tFUS is associated with a risk of minor adverse events approximating 3% (Sarica et al., 2022).

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) (Pasquinelli et al., 2019). 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 behaviour. Indeed, although a recent systematic review of this literature (involving both focused and unfocused ultrasound devices) concluded that there is some evidence to suggest that this technology can change short-term brain excitability and connectivity, induce long-term plasticity, and modulate behaviour, its underlying mechanisms require further exploration (Sarica et al., 2022). For these reasons, to our knowledge tFUS has not been pursued to date in military research.

Table 3: Approaches, Efficacy, Safety & Maturity of tFUS

Transcranial Focused Ultrasound Stimulation (tFUS)	
Approach	A pressure wave of ultrasonic frequencies is used to induce non-invasive, highly localized stimulation of underlying tissue, resulting in suprathreshold neuromodulatory effects.
Efficacy	Primarily clinical applications to date; Limited application for performance enhancement in healthy cohorts.
Safety	Relatively unknown; potential for tissue damage when using high sonication intensities.
Maturity	Approach is immature with no formal clinical certifications exist currently.

2.2.4 Transcutaneous Peripheral Nerve Stimulation

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 (Colzato & Vonck, 2017). 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 (Badran , Dowdle, et al. 2018; Brunyé et al., 2020; Colzato & Vonck, 2017; Tyler et al., 2015).

Invasive stimulation of the vagus nerve reliably alters the release of several neurotransmitters including norepinephrine (NE) and gamma-aminobutyric acid (GABA), as shown with both animal models and humans (Ben-Menachem et al., 1995; Raedt et al., 2011; Smith et al., 2005). More recently, scientists have begun exploring whether non-invasive forms of vagus nerve stimulation, namely transcutaneous auricular vagus nerve stimulation (taVNS), will modulate not only neurotransmitter activity in the brain, but also cognitive, emotional, and/or sensory processing. Transcutaneous VNS is a relatively new, non-invasive method for stimulating the vagus nerve by placing electrodes to target its afferent auricular branch (Ventureyra, 2000). This branch of the vagus nerve projects to brain regions directly innervating the LC, leading some to hypothesize that taVNS may alter NE release. As evidence for such a pattern, Frangos and colleagues demonstrated that taVNS altered brain activity (using fMRI) in the human brainstem and LC, suggesting that it very likely also modulates NE release from the LC (Dolphin et al., 2022; Frangos et al., 2015; George & Aston-Jones, 2010). 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 (Sellaro et al., 2015). 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 (Jacobs et al., 2015), conditioned fear extinction latencies (Burger et al., 2016), divergent creative thinking (Colzato et al., 2018), multi-tasking and inhibitory control (Steenbergen et al., 2015), foreign language learning (Phillips et al., 2021), motor learning (Byczynski & Vanneste, 2023), and memory for the order of words (Kaan et al., 2021). 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) (Badran, Mithoefer, et al. 2018), and reduce sympathetic nervous system activity as indicated by increased heart rate variability (Clancy et al., 2014).

While these neurophysiological and behavioural 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 (Usher et al., 1999), in mediating stress-induced cognitive performance declines (Aston-Jones & Cohen, 2005; Birnbaum et al., 1999), enhancing certain aspects of language learning and memory, and in many clinical disorders (Friedman et al., 1999). Not surprisingly, taVNS has been pursued for its potential in military performance enhancement, particularly by the U.S. Army Research Laboratory (Badran et al. 2018). Most of this research is relatively foundational, affording new understandings of how taVNS affects resting brain activity (Badran, Dowdle, et al. 2018) and cardiac physiology (Badran, Mithoefer, et al. 2018). 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. As this research is pursued, however, it is critical to follow minimum reporting standards established by the international community, including technical characteristics of the device, stimulation parameters applied, and methodological considerations (inclusion/exclusion criteria, outcomes, side effects) to ensure adequate reporting and reproducibility (Farmer et al., 2021).

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. 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 (McGough et al., 2019; Shiozawa et al., 2014), migraine (Magis et al., 2017), and epilepsy (DeGiorgio et al., 2009).

One study showed diverse sympathetic nervous system responses with tTNS in comparison to a sham procedure, that included lower basal sympathetic tone, lower subjective anxiety and tension, and lower heart rate variability response, electrodermal response, and salivary alpha-amylase responses to stress (Tyler et al., 2015). Despite the objective and subjective effects of tTNS on sympathetic nervous system activity, the authors found no evidence that tTNS influenced executive function as assessed by the flanker, Stroop, or n-back tests. Additional research suggests that tTNS can improve sleep quality assessed by actigraphy and reduce anxiety (Boasso et al., 2016).

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

Table 4: Approaches, Efficacy, Safety & Maturity of tPNS

Transcutaneous Peripheral Nerve Stimulation (tPNS)	
Approach	Mild electrical current is applied to peripheral nerves through the skin with the intent of indirectly modulating central nervous system activity.
Efficacy	Modest evidence of cognitive improvement in domains of attention, learning and memory and executive function, as well as reductions in anxiety.
Safety	Generally safe, few known side effects.
Maturity	Approach is mature; newer devices are commercially available; no formal clinical certifications exist currently.

2.2.5 Cranial Electrotherapy Stimulation

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 (Feusner et al., 2012).

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 (Shekelle et al., 2018a,b).

More recently, a very limited number of studies have examined CES for altering affect, physiology, and behaviour 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 (Cupriks et al., 2016; Koleoso et al., 2013; Southworth, 1999; Wagenseil et al., 2018; Winick, 1999).

The physiological, neurochemical, and metabolic mechanisms underlying CES effects are currently unknown. Computational modelling 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 (Black et al., 2004; Datta et al., 2013; Ferdjallah et al., 1996; Feusner et al., 2012; Gense de Beaufort et al., 2012; Lee, Lee, and Park 2019; Schroeder & Barr, 2001).

One theory suggests that CES modulates brain stem (e.g., medulla), limbic (e.g., thalamus, amygdala), and cortical (e.g., prefrontal cortex) regions and increases relative parasympathetic to sympathetic drive in the autonomic nervous system (Gilula, 2007). There is no direct evidence supporting this theory, but one of its assumptions is that CES may induce its effects by stimulating afferent projections of the vagus nerve, which provides parasympathetic signals to the cardiorespiratory and digestive systems.

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 behaviour 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.

Recently, the United States Army DEVCOM Soldier Center conducted a double-blind, placebo-controlled study to examine active versus sham CES effects on biochemical, affective, physiological, and cognitive responses to acute stress exposure. In this study, male participants underwent two sessions, one with active CES administration (20 minutes of stimulation at 100 µA and 0.5 Hz) and the other with sham CES. They were exposed to acute stress while performing challenging cognitive tasks, and their emotional, physiological, biochemical, and cognitive behavioural responses were measured. Cognitive responses included performance on marksmanship, spatial orienting, decision making, and recognition memory. The results showed that the stress induction affected sympathetic adrenal medullary (SAM) activity but not the hypothalamic-pituitary-adrenal (HPA) axis activity (Brunye et al., 2022). However, active CES did not significantly influence emotional, biochemical, or physiological measures. Interestingly, it did enhance performance on a recognition memory test but impaired performance on a perceptual decision-making test. In conclusion, the study found no strong evidence supporting the effectiveness of CES in modulating the immediate nervous system response to acute stress. Therefore, its utility in sustaining performance in high-stress domains, crucial for Warfighters, seems limited.

Ongoing U.S. defence sciences research is assessing whether relatively high intensity and prolonged (20 sessions) dosing of CES might alter physiological activity, endocrine responses, affect, or behaviour during simulated Warfighter-relevant cognitive tasks, in a randomized double-blind placebo-controlled design. 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.

Table 5: Approaches, Efficacy, Safety & Maturity of CES

Cranial Electrotherapy Stimulation (CES)	
Approach	Uses low-intensity electrical current via electrodes placed at bilateral anatomical positions (earlobes, temples) to modulate peripheral and central nervous system activity.
Efficacy	Limited application for performance enhancement in healthy cohorts.
Safety	Relatively unknown; likely similar to TPNS.
Maturity	Approach is immature.

2.2.6 Transcranial Photobiomodulation

Photobiomodulation (PBM) involves the use of near-infrared light (0.75–1.4 µm in wavelength) to modulate cellular activity. In clinical and veterinary settings, PBM has been used to reduce inflammation, alleviate pain, and promote healing (Pan et al., 2023). More recently, applications aimed at modulating neural activity have been explored (Hamblin, 2018). PBM modulates cellular activity through activation of photosensitive enzyme cytochrome c oxidase (COX or Complex IV), the terminal enzyme in the mitochondrial electron transport chain (Hamblin, 2018; Hennessy & Hamblin, 2017; Salehpour et al., 2019). Hamblin (2018) proposed that absorption of near-infrared light by COX produces photodissociation of nitrous oxide (NO), which increases the availability of electrons that can be reduced to oxygen and also increases adenosine triphosphate (ATP) production and mitochondrial membrane potential, which in turn leads to increased neuronal activity (Maiello, 2019). Stimulation of COX also activates transcription factors, which may act as an exercise mimetic (Hamblin, 2018). Currently, PBM is applied either directly via transcranial or intranasal applications, or indirectly through the combined use of near infrared laser and nanodrug carrying particles for more precise delivery of PBM to discrete areas of the brain (Pan et al., 2023). PBM is considered a safe therapy that is relatively free of adverse side effects (Hennessy & Hamblin, 2017), although mild headaches and vivid dreams have been reported (Maiello, 2019).

PBM has most commonly been used to treat physical and cognitive impairments following brain injury or other neurodegenerative processes, such as Alzheimer's and Parkinson's disease (Hennessy & Hamblin, 2017). However, recent evidence suggests that PBM also may be used to improve cognition in healthy adults (Salehpour et al., 2019). For example, PBM has been shown to modulate attention and improve reaction times in healthy adults (Jahan et al., 2019; Barrett & Gonzalez-Lima, 2013). In addition, transcranial infrared laser stimulation targeting the prefrontal cortex produced improved rule-based category learning in healthy adults (Blanco et al., 2017). Significant improvements in motor function, memory performance, and processing speed have also been observed in healthy middle-aged adults following twice-daily application of transcranial PBM compared to placebo (Dougal et al., 2021). PBM was associated with reduced delta frequencies as measured via EEG (Jahan et al., 2019). Zomorrodi and colleagues (2019) also reported reduced delta frequencies as well as higher alpha, beta, and theta wave activity following PBM, which are associated with an increase in alertness and attention (Kučikienė, 2018).

In addition to attention and vigilance, PBM has also been shown to reduce anxiety symptoms in individuals with generalized anxiety disorder when used over 8 weeks (Maiello, 2019), and symptoms of depressed mood in patients diagnosed with major depression (Askalsky & Iosifescu, 2019). In healthy individuals, PBM has been shown to increase functional connectivity between the dorsal lateral prefrontal cortex and amygdala, suggesting greater emotional control, and decreases in negative mood (Alkozei et al., 2021). Indeed, application of PBM has been associated with increased positive affect scores on the Positive and Negative Affect Scale (PANAS) (Barrett & Gonzalez-Lima, 2013).

Table 6: Approaches, Efficacy, Safety & Maturity of PBM

Photobiomodulation	
Approach	Uses near-infrared light (0.75–1.4 µm in wavelength) applied to the head or intranasally to modulate neuronal activity.
Efficacy	Modest evidence of cognitive improvement in domains of attention, learning and memory and executive function, as well as improved mood.
Safety	Generally safe, few known side effects.
Maturity	Approach is maturing; newer devices are commercially available; no formal clinical certifications exist currently.

2.3 NEUROFEEDBACK APPROACHES

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 behaviour (Sitaram et al., 2017). Through the closed-loop process of neurofeedback participants come to learn how to volitionally modulate their own neural activity and behaviour, with potential applications to clinical rehabilitation (Foldes et al., 2015; Renton et al., 2017), therapy (Mayer et al., 2015), and human performance (deBettencourt et al., 2015).

In addition to acute alterations in neural activity, neurofeedback has also been shown to induce relatively long-term changes in both brain structure (grey matter volume) and function (white matter connectivity) (Enriquez-Geppert et al., 2017; Sitaram et al., 2017). For example, one study used 40 sessions of neurofeedback training while participants attempted to modulate a specific EEG signal (right beta amplitude) (Ghaziri et al., 2013), versus a sham (receiving another’s feedback) and control (no intervention) condition. The authors found not only an improvement of visual and auditory attention after neurofeedback training, but one week after training they found increased white matter fractional anisotropy and grey matter volume, in multiple cortical and subcortical brain regions.

There is some additional evidence that neurofeedback can improve foreign language learning (Chang et al., 2017; Chang et al., 2021), short term memory (Nan et al., 2012), visual and auditory attention (deBettencourt et al., 2015;

Ghaziri et al., 2013), confidence judgments (Cortese et al., 2016), perceptual sensitivity (Shibata et al., 2011), motor response speed (Bray et al., 2007), visuomotor tracking ability (Sitaram et al., 2012), athletes' reaction time and decision making (de Brito et al., 2022), creative originality and fluency (especially in those with lower creativity; Agnoli et al., 2018; Gruzelier, 2014), risky decision making (Sourni et al., 2018), and motor skill learning (Zhao et al., 2013).

Several mechanisms have been proposed to explain the effects of neurofeedback on brain and behaviour, including alterations of white matter and myelination (Ghaziri et al., 2013; Ros et al., 2013), activating intrinsic homeostasis and self-organization of the brain (Enriquez-Geppert et al., 2017), promoting a sense of agency and exerting cognitive control (Ninaus et al., 2013), altering default network functional connectivity (Ramot et al., 2016), and activating reward processing networks, control networks, and learning networks (Sitaram et al., 2017).

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 (Dessy et al., 2018; Enriquez-Geppert et al., 2017; Gruzelier, 2014; Scharnowski & Weiskopf, 2015; Sitaram et al., 2017). 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 (Ninaus et al., 2013; Thibault & Raz, 2017).

Despite the uncertainty of the science, international defence 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 (Faller et al., 2019). 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 behaviour (Bassett & Khambhati, 2017). 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 (Sherwood, Kane, et al. 2016; Sherwood, Weisend, et al. 2016).

Table 7: Approaches, Efficacy, Safety & Maturity of Neurofeedback

Neurofeedback	
Approach	A form of biofeedback in which a person monitors their own neural signals (via EEG or fMRI) in real time and then, using auditory or visual feedback, modifies the activity of that signal or a behavior.
Efficacy	Existing evidence supports use for training attention and knowledge acquisition.
Safety	Generally safe; side effects generally associated with monitoring technologies such as EEG or fMRI.
Maturity	Approach is maturing; given need for neural activity monitoring, approach is generally not robust to austere environments.

2.4 FROM SUPERFICIAL TO MEDIAL TARGETS

Established neurostimulation techniques, including those detailed in Chapter 2, are relatively limited in their depth and precision, and are generally used to target relatively superficial regions of the cerebral cortex (Bestmann & Walsh, 2017). This is an important consideration given the relevance of multiple subcortical structures for shaping Warfighter behaviour, including the thalamus and hypothalamus, hippocampus and parahippocampus, amygdala, and basal ganglia. With TMS, which has relatively high focality at target for brain regions within centimetres of the cortical surface, directly stimulating relatively deep cortical targets is only possible with relatively wide electric fields that limit focality (Deng et al., 2013, 2014). Similar results have been found with tES, demonstrating that stimulation administered with conventional scalp electrodes can reach deep brain regions (e.g., subthalamic level) but with very diffuse electric fields (Chhatbar et al., 2018; Shahid et al., 2014). While diffuse, these effects appear to carry biological relevance for neural activity and behaviour (Khan et al., 2020; Nonnekes et al., 2014), though it is difficult to model and predict the nature of any such effects.

There are two general approaches for increasing focality of generated electric fields at subcortical targets: indirect targeting and direct targeting. Two indirect targeting approaches are worth considering. First, transcranial temporal interference stimulation manipulates the frequency properties of pairs of sinusoidal electrical currents administered simultaneously via an array of four scalp electrodes (Grossman et al., 2017). This approach delivers sinusoidal electrical waveforms at frequencies above the dynamic range of neural firing (i.e., ≥ 1000Hz), and the intersection of those two waveforms results in a difference frequency produced in an envelope encompassing deep brain structures. If this difference frequency is within the dynamic range of neural firing, it can be used to modulate activity of neural populations residing within the envelope. While this approach is promising in animal models and simulations, (S. Lee et al., 2020; X. Song et al., 2021), it has not yet been validated in humans (Liu et al., 2022). A second indirect approach involves stimulating a superficial node of a functional brain network with the aim of modulating activity in distant (and potentially deep) connected regions. For example, modulating the primary motor cortex (M1) with tDCS results in changes to both intrahemispheric and interhemispheric neural activity across diverse functionally connected brain regions (Polanía et al., 2011), and modulating the parietal cortex with tACS results in changes to neural activity across diverse nodes of the default mode network (DMN) and rich club network (Tesche & Houck, 2019). Similar results have been found with TMS, including indirect activation of local and remote functionally connected networks residing at both cortical and subcortical levels (Bergmann et al., 2021; Oathes et al., 2021).

Recent advances in low-intensity focused ultrasound (LIFU) have highlighted the potential for directly targeting subcortical structures with non-invasive neurostimulation (Darmani et al., 2022). This relatively new method, LIFU, has been shown effective for exciting or inhibiting subcortical neuronal activity in both animal models (Folloni et al., 2019) and humans (Legon et al., 2018), and shows spatial focality at depth exceeding TMS and tES (Bystritsky et al., 2011; Dallapiazza et al., 2017). A recent study using LIFU in humans targeted the left basal ganglia and measured blood oxygenation level dependent (BOLD) signals and arterial spin labelling (ASL) with functional magnetic resonance imaging (fMRI) (Cain et al., 2021). The study showed three primary results. First, LIFU reliably activates targeted subcortical structures both during stimulation and immediately after stimulation, producing a lasting effect. Second, LIFU appears to induce inhibitory effects, at least at their selected frequency (10-100Hz with a 650 kHz carrier wave), in targeted local (and distal) brain regions. Third, LIFU parameters including pulse frequency and width, appear to be important parameters for predicting effects in subcortical regions both during and following stimulation. Together, these recent results suggest that LIFU is a promising new technology and methodology for selectively and reliably altering subcortical activity in humans. To our knowledge, no research to date has assessed how subcortical LIFU affects human performance, but it remains an exciting opportunity for continuing research.

2.5 FROM STRUCTURES TO SYSTEMS

Our review of neuromodulation techniques demonstrates that research in this area typically begins with using neuroimaging and neurophysiological techniques to identify brains structures that underlie specific cognitive functions, and then selecting a neuromodulation technique to manipulate their activity to modulate the specific cognitive functions of interest. However, one of the major advances in systems neuroscience has involved the discovery of a limited number of large-scale networks (rather than isolated structures) that support cognition (Buckner et al., 2013). These networks have been discovered using resting-state connectivity, which is a technique using which one can identify brain regions that exhibit similar patterns of fMRI activity fluctuations (i.e., intrinsic oscillatory dynamics), and can therefore be grouped into large-scale brain systems called “networks.” The 6-7 discovered networks to date include the executive control network that underlies cognitive control, the default-mode network that underlies internally generated thought such as mind wandering and daydreaming, and the salience network that underlies orienting to environmental cues that are relevant for survival. Other networks include the somatomotor, visual, language, and dorsal attention networks.

An important technological and conceptual advance in neuroimaging research has involved the use of this technique to study the spatiotemporal interactions (i.e., dynamics) of these large-scale brain networks in the service of various types of thinking, such as creative cognition (see Zabelina & Andrews-Hanna, 2016). As a result of this research in systems neuroscience we now know that cognitive functions such as attention are underpinned by large-scale networks rather than isolated structures, and that there is functional connectivity (both positive and negative) between networks in support of higher-order cognitive functions that draw on multiple systems (e.g., reasoning). This evidence suggests that targeting a specific structure cannot be done without taking into consideration the possible effects of this intervention on the network within which it resides, as well as the other networks that it is functionally connected to. Indeed, considerations of functional connectivity are necessary for generating a realistic representation of the impact of neuromodulation on brain activity, even if the target includes a single structure in the brain.

Table 8: Known Influences of Neuroenhancement Techniques on Cognitive Domains

		Cognitive Domain						
		Sensation & Perception	**Attention**	**Executive Functions & Working Memory**	**Learning & Long Term Memory**	**Language**	**Motor & Procedural Function**	**Other**
Technique	**TMS**	Improved perceptual discrimination; improved somatosensation	Improved spatial orienting; reduced involuntary attentional capture	Improved executive control (inhibition)	Improved motor skill acquisition/ learning; enhanced long term potentiation	Improves lexical decision speed with abstract words	Improved visual search and object identification; improved motor speed (response times)	Improved reasoning; improved creativity
	tES	Improved visual perception; improved visual perceptual learning	Improved complex attention	Improved adaptive cognitive control, working memory, and decision making	Improved declarative memory; improved long-term memory	Improved recall of action sentences; improved comprehension of simple and complex sentences.	Improved perceptual-motor function; faster response times; accelerated motor learning, motor adaptation and procedural learning	Improved emotion regulation; improved creativity; improved theory of mind; improved target detection in complex visual search tasks
	tFUS	Improved sensory discrimination	Improved attention (reduce attentional capture); sustained attention	**No known effects for non-clinical human performance.**	**No known effects for non-clinical human performance.**	**No known effects for non-clinical human performance.**	Improved motor behaviour	Improved positive mood, emotion regulation
	TPNS	**No known effects for non-clinical human performance.**	Improved attention (executive control/multitasking)	Improved inhibitory control	Improved associative memory (face-name),	Improved foreign language learning, and memory for word order	Improved motor task learning	Reduced anxiety; improved divergent thinking (creativity)
	CES	**No known effects for non-clinical human performance.**	Improved sustained attention	**No known effects for non-clinical human performance.**	**No known effects for non-clinical human performance.**	**No known effects for non-clinical human performance.**	Increased muscle force output	Reduced perceived anxiety
	PBM	**No known effects for non-clinical human performance.**	Improved alertness, attention and vigilance	Improved processing speed	Improved rule-based category learning; improved short-delay memory	**No known effects for non-clinical human performance.**	Improved reaction times	Reduced anxiety and depression
	NF	Improved perceptual sensitivity	Improved visual and auditory attention	Improved working memory	Improved short term memory	Improved foreign language learning	Improved motor response speed, visuomotor tracking ability, motor skill learning	Improved creativity; improved risky decision making

Chapter 2 – REFERENCES

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Chapter 3 – METHODOLOGICAL CHALLENGES FOR COGNITIVE NEUROENHANCEMENT

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3.1 BACKGROUND

As with any nascent scientific discipline, several methodological and conceptual challenges exist that make it difficult to envision near-term application of neuroenhancement technologies to military training or operations. The field of neuroenhancement research faces several challenges that impact its validity and reproducibility. This chapter discusses key issues related to the risk of bias, reproducibility, parameter heterogeneity, conflicts of interest, and the measurement and accounting of individual differences. The replication crisis in the psychological sciences has raised concerns about the reliability of research findings, and neuroenhancement studies are not immune to these challenges. The inconsistent replication of results, small sample sizes, and limited methodological details have been identified as common issues in various neuroenhancement techniques. Moreover, conflicts of interest arise when research is influenced by financial gain or involvement with the manufacturers of neuroenhancement technologies. Another significant challenge is the high heterogeneity of parameters used in different neuroenhancement techniques, making it difficult to optimize and compare outcomes. Lastly, individual differences, such as baseline cognitive performance and other factors, can impact the efficacy of neuroenhancement interventions. Addressing these challenges is crucial for improving the validity and applicability of neuroenhancement research in both laboratory and real-world military settings.

3.2 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 (Kessler et al., 2012), with substantially fewer participants experiencing them with taVNS (Redgrave et al., 2018). Several methodological features of neurostimulation influence the likelihood of a participant experiencing uncomfortable sensations, with higher chances when using direct current than alternating current, as stimulation intensity increases, electrode surface area decreases, or electrode contact quality (impedance) decreases (Ambrus et al., 2010; Antal et al., 2017; Bikson et al., 2016; Bikson et al., 2009). Any such effects tend to be short-lived and mild to moderate in subjective intensity. In addition to uncomfortable skin sensations, electrical burns can also occur with misapplication of the device. With transcranial electrical stimulation, serious adverse events or irreversible injury rates are reportedly absent when considering over 30,000 sessions of data from research using conventional tDCS protocols (i.e., intensities ≤ 4mA, duration ≤ 40 min) (Bikson et al., 2016). As consumer-grade transcranial and transcutaneous electrical stimulation devices continue to proliferate the market, it is likely that the home-use of these devices will lead to a rise of reported adverse side effects.

With TMS, risks include seizure induction, hypomania, headache or local pain, hearing changes, burns from electrodes, or excessive brain tissue heating (Rossi et al., 2009). 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 (Loo et al., 2008) and the other risks are negligible or otherwise unreported (Rossi et al., 2009). A review of the U.S. Food & Drug Administration's Manufacturer and User Facility Device Experience (MAUDE) database revealed over 50 reported adverse events over the past 5 years, primarily pertaining to skin irritation, seizures, loss of consciousness, anxiety, sleep disturbances, migraines, vertigo, and twitching limbs.

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 (Legon et al., 2020). 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 (Pasquinelli et al., 2019).

With CES, the most frequently reported side effects are vertigo, skin irritation, and headaches (Kirsch & Nichols, 2013), which are estimated to occur about 1% of the time (Kirsch et al., 2014). 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 research settings 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 (McClure et al., 2015; Mischoulon et al., 2015).

An FDA-commissioned review of the safety of CES by the National Research Council (1974) stated, “significant side effects or complications attributable” to the application of electric current of approximately one milliampere or less for “therapeutic effect to the head” (i.e., cranial electrotherapy stimulation) were “virtually non-existent” (p. 42). To examine adverse events reported to the FDA by device users, we searched the FDA MAUDE database for records between 1990 and 2020 for the CES devices listed in Section 1.2. Three adverse reactions were reported during or following the use of an Alpha-Stim CES device, one in 2012 for burns experienced on earlobes, one in 2013 for onset of severe tinnitus, and one in 2019 for severe gastrointestinal distress and insomnia. Seven adverse reactions were reported during or following the use of a Fisher Wallace CES device, including for disorientation, vestibular problems (balance, coordination, dizziness, vertigo), headaches, tinnitus, anxiety, depression, fatigue, brain haemorrhage, and death.

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.

3.3 COCHRANE CRITERIA & RISK OF BIAS

The Cochrane Risk of Bias (version 2) tool provides a mechanism for formalizing risk of bias that may be present in randomized trials (Higgins et al., 2011). 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. We cover each of these, in turn.

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 (Hotermans et al., 2008). Similar reporting deficiencies were found when examining studies using tDCS (Dedoncker et al., 2016), taVNS (Clancy et al., 2014), and CES (Kavirajan et al., 2014).

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 (Dedoncker et al., 2016). Even with participant blinding, differences in skin irritation between active and sham tDCS conditions can cause participants to become aware of their assigned intervention (O’Connell et al., 2012). The most used sham method in tES studies involves ramping up sham stimulation to match active stimulation intensity (e.g., 2mA) and then ramping down (usually over the course of 1 min); this ramping-up and down procedure is typically done at the beginning and end of the stimulation session. If participants are probed for perceived sensations at the peak of the ramp-up period, sham and control conditions are well matched for sensation; however, if they are probed at any other time during stimulation, there are large differences in perceived sensation across the two conditions (Brunyé et al., 2014). These effects are 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 (Lee et al., 2016), and sham TMS procedures can induce sensory and motor side effects that can selectively and reliably alter task performance (Duecker & Sack, 2015).

Continuing research should focus on developing more effective sham procedures to ensure adequate blinding. In the tES domain, this might include matching cutaneous sensation across sham and active conditions throughout session durations; ongoing research by the United States Army is exploring whether arcing current across the scalp within highly proximal (i.e., <1cm separation) electrode sites may induce cutaneous sensations that match active sensations without electrical current penetrating the skull. Additional methods involve leveraging potential specificity of neuromodulatory effects by dissociating stimulation effects over brain regions putatively involved versus uninvolved in outcome task performance, inducing polarity-specific effects with matched cutaneous sensations, or using between-participants designs that may or may not mitigate awareness of conditions (given no relative knowledge). Of course, scientists must balance their selection of sham methodologies with emerging science indicating non-specific and diffuse electrical current propagation through the cortex (Miranda et al., 2013; Miranda et al. 2006; Neuling et al., 2012; Wagner et al., 2007), and the logical challenges associated with inferring functional independence of brain regions based on neuroimaging data (Hanson & Bunzl, 2010; Poldrack, 2008). In other words, each sham methodology has its own pros and cons that must be considered during selection and reporting, and innovative sham procedures are needed to help overcome these challenges. Beyond sham procedures, researchers need to exercise caution to ensure they are measuring and perhaps standardizing participant expectations regarding tES effects; indeed, altering participant expectations regarding the outcomes of tES can alter the extent of advantages seen on executive function tasks following tDCS targeting the dlPFC (Rabipour, Andringa, et al. 2018; Rabipour, Wu, et al. 2018).

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, PBM, 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 behavioural and neuroscientific outcomes of tES in separate publications with different exclusion criteria (Conley et al., 2015), reporting subjective and objective measures of neurofeedback effects in separate publications (Garrison et al., 2013), and excluding participants from analysis without ample statistical justification (Mauri et al., 2015). It is difficult to derive comprehensive understandings of neuroenhancement effects on brain and behaviour when outcomes are not fully reported or are variably reported across publications.

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 (Auer et al., 2015; Hamilton et al., 2010; Sitaram et al., 2017). Indeed, selecting appropriate measures of near-, medium-, and far-transfer through formal taxonomy is important but also very challenging (Barnett & Ceci, 2002; Brunyé et al., 2020). Additional challenges include selecting outcome tasks that are not only well-suited to the hypothesized effect of a manipulation but are also reliably sensitive to exogenous influences, and effectively dissociating performance on multiple tasks in order to assess the specificity of neuroenhancement effects.

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 (Imburgio & Orr, 2018). 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 (Chambers et al., 2015). Neuroenhancement research would benefit from this mechanism that helps reduces the inherent disincentivizing of null or unexpected results.

3.4 REPRODUCIBILITY

Scientists have considered the disproportionately positive results published in the psychological sciences, leading to what some have considered a "replication crisis" (Maxwell et al., 2015). 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" (Ioannidis, 2005). 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) (Earp & Trafimow, 2015; Neuliep & Crandall, 1993). Between these two is a more progressive perspective that suggests that even apparent failures to replicate might be informative for progressing experimental methods and theory (Earp & Trafimow, 2015).

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 (Meehl, 1990). 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 (Protzko & Schooler, 2017).

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 (Sulzer et al., 2013), excessively small sample sizes (Boynton, 2001), and limited reproducibility (Schabus et al., 2017). Similar criticisms have arisen in the context of tES (Brem et al., 2014; Horvath et al., 2015a, 2015b), TMS (Belardinelli et al., 2019; Ji et al., 2019; Ridding & Ziemann, 2010), CES (Kavirajan et al., 2014; O'Connell et al., 2011), and transcutaneous peripheral nerve stimulation (Burger et al. 2016; Warren et al. 2019). 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 (Button et al., 2013). Second, scientists, institutions, and publishers should assign equal value to manuscripts reporting null or counter-intuitive results, assuming sample size criteria are met (Martin & Clarke, 2017; Schooler, 2011). 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 (Francis, 2012). Third, registered reports and open access data sharing are an effective tool for reducing publication bias and increasing the transparency and reproducibility of science (Schooler, 2011).

3.5 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 (Thut & Pascual-Leone, 2010). With tES, parameters include the number and type of electrodes, the stimulation sites, and the timing, intensity, frequency, and duration of stimulation (Bikson et al., 2016; Dedoncker et al., 2016; Hill et al., 2016). Similar 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 modelling 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.

3.6 CONFLICTS OF INTEREST

When professional judgments or activities, such as selecting experimental conditions or which data to analyse and report, are affected by a secondary interest such as financial gain, conflicts of interest (COI) can occur (Field & Lo, 2009). 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 (Gilula, 2007; Kirsch et al., 2014; Kirsch & Chan, 2013; Kirsch & Gilula, 2007; Kirsch & Nichols, 2013; Kirsch & Smith, 2000). 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.

3.7 MEASURING AND ACCOUNTING FOR INDIVIDUAL DIFFERENCES

Differences across studies in the effectiveness of neuromodulation techniques has brought to the light the role individual differences play in assessing the efficacy of these techniques (e.g., Berryhill et al., 2014). Recent reviews of studies utilizing neuromodulation techniques to alter cognitive function have identified differences in outcomes across studies (see Westwood & Romani, 2017; Horvath et al., 2015). The inconsistency in findings have been attributed to inconsistent methods used across studies (e.g., brain region targeted, duration of stimulation) as well as individual differences. Individual differences that may impact the outcomes of neuromodulation include baseline cognitive performance, expertise with a task, trait differences, and structural or physiological differences. By measuring and accounting for these individual differences, neuromodulation techniques may be improved.

3.7.1 Baseline Cognitive Performance

Any neuroenhancement technique or technology must make both a practical and statistical improvement in cognitive performance beyond baseline. To quantify any enhancement effect, it is necessary to base measurements upon gold-standard laboratory research methods; however, in the military sphere, it is also important that an enhancement is practically useful and makes a meaningful difference to job/role performance in the real world (i.e., is ecologically valid). For example, while laboratory experiments are usually structured and time-limited (as is often required by institutional ethics committees), real-world task/role performance may have a much longer timeline. A robust understanding, therefore, of performance over variable timelines would also be essential. To this end, it is important to obtain performance measurements representing a holistic view of human cognitive performance as compared to baseline performance on tasks in – at minimum - a realistic scenario before any enhancement technique or methodology is recommended for operational testing and/or use.

Demonstration of statistical significance in experimentation is critical to stating any cognitive performance enhancement effects are real, and characteristics common to military cognitive performance research make determination of statistical significance more complex. In experimental conditions – for example in psychological and neurotechnology research – it is common to average results across a large N to develop baselines and experimental effects, thus improving statistical validity. However, measuring the effect of interventions on military task performance typically demands that individual performance is defined and improved, rather than group performance; additionally, low N is common. This complicates the design of experiments and analysis of data from any such research. These aspects should be made especially clear to military customers who are often swayed by media reports of 'significant' effects from applied neuroenhancement technologies, whose analytic and algorithmic approaches are commonly not transparent when determined to be proprietary. Both statistical and practical comparisons to baseline cognitive performance should be built into any neuroenhancement research conducted for military operational uses.

In an experimental condition, it is common to set 'baseline' as performance against a control condition, while in real life baseline brain activity and performance can vary throughout each day, between days, and between individuals. To address this, many research groups are now turning to closed-loop systems which maintain a baseline model of brain activity and outputs upon which performance can be compared. These systems are very new, and require complex AI to support them, but they probably provide the only hope of individual comparisons to baseline for future neuroenhancement research.

Differences in baseline cognitive performance have been shown to influence the likelihood of a neuromodulation technique to improve specific task performance. For example, individuals who already demonstrate high performance on a specific task have been shown to not improve performance beyond their baseline performance (e.g., Berryhill & Jones, 2012; Jones & Berryhill, 2012; Berryhill et al., 2014; Gözenman & Berryhill, 2016; Sela et al., 2012; Tseng et al., 2012; Hsu et al., 2014, 2016; Jones et al., 2015; London & Slagter, 2015). By evaluating baseline task performance on the task targeted for enhancement, researchers can account for the effect of that individual difference. For example, Splittgerber et al. (2020) compared baseline performance to later performance on a working memory task to assess how multichannel tDCS altered performance. They demonstrated that those with worse baseline performance benefited from the application of tDCS. Moreover, Splittgerber et al. also found that individuals with higher baseline performance demonstrated worse performance following the application of tDCS.

3.7.2 Task Expertise

Having existing expertise in performance of a task results in the ability to complete said task more effortlessly to begin with. This ease in task completion has been associated with different neuronal activation patterns, including a reduction in the activation of neural resources, and in some cases a redistribution of the brain regions activated (e.g., Neumann et al., 2016). Recent research has demonstrated that differences in expertise affect the outcomes of tDCS, likely due to these individual differences in neuronal activation patterns. For example, expertise has been found to play a significant role in the outcome of the application of tDCS when examining sensory-motor skill in esports (e.g., Toth et al., 2021) and jazz pianists (e.g., Rosen et al., 2016). These studies demonstrated that the application of tDCS preferentially improved performance amongst novices compared to experts, and even hindered performance in the experts in the jazz pianist study. Such findings suggest that the use of neuromodulation techniques for improving performance may be limited to those who are still novices and thus be used to accelerate learning. Alternatively, it may be that due to the redistribution of the brain regions used to complete a task, different stimulation settings are needed to aid in the improvement of performance in experts. Measuring experience or expertise with a task can be as simple as requesting the participant to report amount of time spent with a task, as often used in aviation to identify pilot expertise, or as involved as having a participant complete a baseline iteration of a task. When measuring cognitive task performance, assessment of baseline performance is oftentimes a preferred method (as discussed previously). Accounting for task expertise will likely be more critical when considering the applied use of neuromodulation techniques.

3.7.3 Trait Differences

Various trait factors are known to impact performance on cognitive tasks, and recent research has suggested may also affect how responsive an individual is to neuromodulation. Motivation is a trait that received attention in recent studies, with several researchers identifying that those who score higher on this trait have been more responsive to the effects of tDCS (see Di Rosa et al., 2019; Metuki et al., 2012; Sela et al., 2012; Jones et al., 2015). The Behavioural Inhibition System/Behavioural Approach System (BIS/BAS) scale (Carver & White, 1994) has been used to measure motivation, with the BAS component of the scale examined. The measure of the BAS is thought to be reflective of the neurophysiological mechanisms for reward sensitivity, and thus the scale can be used as a proxy to determine someone's sensitivity within these areas.

3.7.4 Physiological Differences

Recently, several differences in underlying physiology have been explored as a means of understanding the mechanisms by which neuromodulatory techniques work, as well as to determine individual differences that may impact outcomes. From this work, a variety of physiological differences have emerged, ranging from neurochemical differences to neurophysiological differences. Filmer et al. (2019) evaluated how differences in baseline neurochemical excitability may affect the behavioural outcomes of tDCS. They found that pre-stimulation measures of GABA and glutamate were correlated with behavioural outcomes following the application of tDCS.

In addition to neurochemical differences, skull thickness has been shown to also impact the outcomes tDCS. Opitz et al. (2015) demonstrated that skull thickness can impact the electric field strength within the brain when applying tDCS. By altering the electrode placement on a constructed head model, they found that when the electrode was placed over the thinner skull regions, the current passed through resulted in higher electric field strengths. Similarly, the presence of head fat has also been shown to affect the electric field distribution of tDCS (Truong et al., 2013). More recently, Zanto et al. (2021) explored the effects of individual differences in neuroanatomy and neurophysiology while applying tACS. They found improved task performance when they accounted for individual differences in neuroanatomy via fMRI measurements. The practical implication behind these differences is that different intensities of the current applied will result in different electrical field magnitudes, thus impacting whether there is an inhibitory or excitatory effect.

Finally, in terms of important individual differences, there is increasing evidence to suggest that both sex and gender must be taken into consideration to generate accurate frameworks for studying health and performance in humans. In this context, sex usually refers to the biological aspects of maleness or femaleness, whereas gender implies the psychological, behavioural, social, and cultural aspects of being male or female (i.e., masculinity or femininity). For example, both sex and gender can influence the epidemiology of injuries with cognitive sequelae, such trajectories of recovery following mild TBI (Colantonio, 2022; Mollayeva, 2021). This suggests that to the extent that any neuromodulation or neurofeedback intervention might be used to enhance cognitive performance following mild TBI, it is important to take both sex and gender into consideration.

3.8 MEASURING AND ACCOUNTING FOR STATE-RELATED DIFFERENCES

Understanding and measuring the transient states experienced by Warfighters is crucial when considering the selection and application of neuroenhancement techniques. Transient states such as stress, emotional states, physical exertion, sleep, dehydration, thermal load (cold and hot), and nutritional deprivation can significantly impact a Warfighter's ongoing cognitive and physical performance. By comprehending these transient states and understanding how they can predict performance outcomes, researchers and practitioners can better select between and tailor neuroenhancement interventions to meet the specific needs of individuals in real-time situations.

For example, research demonstrates that acute stress can alter the ability to process and remember spatial information that might be critical to navigation tasks, varied emotional states can change people’s level of focus on different aspects of an environment or task, and sleep deprivation can diminish sustained vigilance. Measuring ongoing states and understanding how they link to expected performance can afford the timely and relevant application of appropriate techniques, ensuring that the interventions are effectively targeted to Warfighters’ current circumstances. Furthermore, it is also possible that certain neuroenhancement interventions are of varied effectiveness under certain circumstances; for example, enhancement techniques designed to reduce stress responses may not be suitable for personnel in sleep deprived low arousal states, and techniques designed to increase vigilance may not be suitable for personnel in high arousal or stress states.

By considering these factors, researchers and practitioners can set realistic expectations for the outcomes of neuroenhancement techniques, enabling better planning, training, and decision-making in military contexts. Ultimately, the comprehensive understanding and measurement of transient states contribute to enhancing Warfighters' performance, safety, and overall mission success.

3.9 TRANSLATIONAL RESEARCH FROM LABORATORY TO FIELD

Moving neuromodulatory enhancement techniques from the laboratory to the field is a critical component for the realization of these techniques for the Warfighter. However, to date, little such research exists. Of the existing research to date, only examination of the effects of tES on applied tasks is available. To the knowledge of the authors, no studies have yet been completed within field settings. Brunyé et al. (2019) summarized the literature regarding the use of tES to modulate applied task performance. In this summary, the applied tasks included: simulated air traffic control (Nelson et al., 2016), threat detection and identification (Parasuraman & McKinley, 2014), learning to identify concealed objects (Clark et al., 2012), navigation of a virtual environment (Brunyé et al., 2014, 2018), and simulated driving (Beeli et al., 2008a, 2008b; Sakai et al., 2014). Each of the aforementioned studies examined the outcomes of simulated task performance after receiving some type of tES intervention. While these examples of altered or enhanced applied task performance are promising, for example reducing the time to learn to identify concealed objects (Clark et al., 2012), they do not yet provide the necessary evidence that this technology is ready to transition to applied settings for military use. For that, applied research is needed to fully evaluate the effects of these interventions on applied performance. Recently, Feltman et al. (2021) used tDCS during a simulated flight in US Army aviators. In their study, the application of tDCS to the right posterior parietal cortex during the flight resulted in the aviators maintaining their approach to landing performance. This study suggests tDCS may be effective in altering performance on applied tasks; however, further studies are needed to determine the reliability of such interventions.

Besides demonstrating the utility of these interventions on applied task performance, other challenges exist for translating this research from the laboratory to the field. One such challenge is the availability of field-ready devices. Many of the devices used in research are bulky or require dedicated power supplies and do not lend themselves well to use in an applied setting. There are some commercially developed devices that are marketed for at-home use for to treat depression. These devices are worn like a headband. Given that these devices already exist for use outside of the laboratory, there is promise for being able to obtain a device that could be used in the field with healthy, neurotypical participants. However, one concern with the currently available devices is that they would not be able to fit beneath a helmet. Given that much of the literature suggests neuromodulation interventions such as tDCS are most effective when applied during a task (e.g., Katsoulaki et al., 2016), not being able to integrate the device into a helmet is a drawback.

Chapter 3 – REFERENCES

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Chapter 4 – IMPORTANT CONSIDERATIONS FOR COGNITIVE NEUROENHANCEMENT

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4.1 BACKGROUND

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 behaviour (Chatterjee, 2013). This chapter delves into the ethical considerations surrounding neuroenhancement. It highlights the principles of beneficence, autonomy, and justice as crucial factors to consider when evaluating the ethical implications of neuroenhancement. It also explores the challenges of calculating cost-benefit analyses and the potential long-term consequences of neuroenhancement. Additionally, it discusses the legal implications, distinctions between excellence in process versus outcome, threats to societal notions of personhood, and the lack of regulatory oversight in this field. Finally, the chapter emphasizes the need for policies and procedures in military contexts to ensure safety, beneficence, and protection of individual autonomy.

4.2 ETHICAL CONSIDERATIONS

One common way to conceptualize the ethical implications of neuroenhancement is, in addition to safety, to focus on the following principles: beneficence, autonomy, and justice (Beauchamp, 2003).

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 (Beauchamp, 2019). 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 (Chatterjee, 2013). 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 (Russo et al., 2013), in other cases the outcomes might be unknown. Indeed, any intervention designed to exogenously alter brain activity, thought, character, and behaviour 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 (Chatterjee, 2013). 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 (Caplan, 2003).

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 (Chatterjee, 2013; Wade, 2018), distinctions between excellence in process versus outcome (Goodman, 2010), and potential threats to society's notions of personhood (Chatterjee, 2013). There is also a gap in regulatory oversight of neuroenhancement techniques, particularly relative to other stimulants and pharmaceuticals intended to enhance performance (Jotterand & Dubljević, 2016), 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.

4.3 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 (Bestmann et al., 2015; Brem et al., 2014). Many modern theories rely on sliding scale models, which postulate that anodal stimulation increases neuronal excitability (depolarization), and cathodal stimulation does the opposite (hyperpolarization) (Bestmann et al., 2015).

One sliding scale model, the zero-sum model, suggests that stimulation causes a net zero-sum gain through antagonistic modulation of various brain regions (Brem et al., 2014). 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 (Luber, 2014; Luber & Lisanby, 2014). 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 (Dosenbach et al., 2008; Zanto & Gazzaley, 2013) via tES targeting the dlPFC could induce a redirection of metabolic resources away from other brain networks, such as the salience network (Chen et al., 2016). 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 behaviour, how long any such costs might last, and whether they are reversible in all situations.

Continuing research at the intersection of cognitive and defence 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.

4.4 POORLY DEFINED AND QUANTIFIED PSYCHOLOGICAL CONSTRUCTS, INCLUDING WAYS OF MEASURING TRANSFER

To assess the impact of any neurological intervention on cognitive performance, it is first and foremost necessary to have a valid and reliable measure for the psychological construct that forms the target of the intervention. For example, if one were interested in quantifying the impact of tDCS on reasoning, it would be necessary to have a specific conceptual definition of the specific type of reasoning that is of interest (e.g., deductive reasoning), and an operational definition which would specify how one would go about measuring it (e.g., accuracy in syllogistic reasoning). In addition, it is also necessary to have an accurate psychological measurement of whether transfer has or has not occurred. As it turns out, historically, within the discipline of psychology both requirements have proven difficult to realize, for various reasons. In this subsection we will highlight several difficulties in measuring psychological constructs accurately—ranging from the theoretical to the methodological—that can make the precise quantification of psychological constructs difficult. In addition, we will discuss the ways in which the measurement of transfer can be problematic, including ways to improve that process.

Difficulties in the measurement of psychological constructs can arise very early in the conceptualization process and can have many sources. One source of the problem may be the presence of multiple theoretical perspectives regarding the same construct, meaning that the same psychological construct is conceptualized differently based on the specific theory within which it resides. In turn, this can affect the way in which it is measured. In such cases the problem is not a lack of clarity or precision per se, but rather the absence of a measure that reflects a uniform understanding of the psychological construct under consideration. For example, in their review of the literature on executive functions, Chan et al. (2008) noted that this term "is an umbrella term comprising a wide range of cognitive processes and behavioural competencies which include verbal reasoning, problem-solving, planning, sequencing, the ability to sustain attention, resistance to interference, utilization of feedback, multitasking, cognitive flexibility, and the ability to deal with novelty" (p. 201). Furthermore, they also noted several different theories of executive functions (e.g., Luria's theory, supervisory attentional system [SAS], Stuss and Benson's tripartite model, Duncan's goal-neglect theory, Goldman-Rakic's working memory model, etc.), which attach variable weights to the aforementioned processes within their structure. It is therefore critical that when researchers focus on the enhancement of executive functions, that there be well-defined theoretical reasons for adopting one theory over others, and careful selection of the tests that measure each of its subcomponents. Similarly, it is important to understand the constraints that govern the extension of inferences drawn from any specific theory/measure of executive functions to other theories/measures of executive functions. Doing so will ensure that inferences remain valid within the context in which they apply.

An additional possible factor that can contribute to poorly defined and quantified psychological constructs refers to a lack of conceptual/theoretical precision and specificity with which constructs are defined, and the downstream difficulties with their measurement that can follow as a result. For example, recently, "in an effort to promote clear thinking and clear writing among students and teachers of psychological science by curbing terminological misinformation and confusion," Lilienfeld et al. (2015, p. 1) published a provisional list of 50 commonly used terms in psychology and psychiatry that should be avoided, or at most used sparingly and with explicit caveats. The problematic terms fell into one of five categories (i.e., inaccurate, or misleading terms, frequently misused terms, ambiguous terms, oxymorons, and pleonasms), and included mainstays of psychological and psychiatric discourse including "comorbidity" and "latent constructs," among others. The article was meant to highlight the widespread use of terms that the authors believed do not possess sufficient specificity and clarity for scientific discourse. Although one could argue about the contents of that specific list, it is nevertheless true that as scientists we should strive to rely on terminology that is well defined and quantified. To the extent that any construct does not meet this requirement, its use should be avoided or limited.

Even when our psychological constructs themselves are well defined, the act of measurement itself can still suffer from method variance—defined as variance that is attributable to the measurement method rather than to the construct the measure represents. In their extensive review of method variance, Podsakoff et al. (2003) have identified several major sources of method variance, including common rater effects (i.e., when the respondent providing the measures of the predictor and criterion variables is the same person), and item context effects (i.e., when the context in which the assessment is conducted influences the relationships under consideration), among others. Critically, the authors also provide prescriptions on how to address these important types of biases in measurement. As they note, awareness regarding the effect of method variance, which is rather prevalent in psychological research, "requires carefully assessing the research setting to identify the potential sources of bias and implementing both procedural and statistical methods of control" (p. 900). Their work on method variance highlights the care that should be given to the choice of measurement methods to minimize sources of error in assessment.

Finally, and of particular importance to the present NATO group, enhancement studies necessitate that there is an accurate psychological measurement to determine whether transfer has or has not occurred. In their influential and comprehensive assessment of this question, Barnett and Ceci (2002) reviewed the transfer literature and argued that an important reason why agreement regarding the success (or failure) of transfer has been difficult to achieve is that researchers have meant different things when they have used the term transfer—and by extension what is meant by far vs. near transfer. They argued that what the field needs is an agreed-upon set of dimensions based on which researchers can specify the precise conditions that characterize each transfer scenario, thereby enabling informed discussion and inferences. Toward that end, they proposed nine dimensions, which could be broken down into two broad categories: Content and context. Content dimension are used to specify what was transferred: (1) learned skill (what is the specificity/generality of the learned skill: procedure, representation, or general principle/heuristic), (2) performance change (the measure against which performance is measured: speed, accuracy, or approach to the task), and (3) memory demands (does the transfer task requires the execution of a learned activity only, or are there additional memory demands: execute only, recognize, and execute or recall, recognize, and execute). In turn, context dimensions are used to specify the contextual conditions under which transfer was assessed: (4) knowledge domain (are the training and transfer domains similar or different?), (5) physical context (did training and transfer testing occur in the same physical location?), (6) temporal context (what was the time lag between the end of training and transfer testing?), (7) functional context (which mindsets do the training and transfer skills evoke in the person?), (8) social context (are training and transfer testing administered individually or in groups?), and finally (9) modality (what are the modalities of the training and transfer tasks?). Recently, Vartanian et al. (2021) applied Barnett and Ceci's (2002) taxonomy to assess the literature in relation to NeuroTracker—a 3D multiple object tracking technology aimed at training attention and memory—to understand the conditions under which it does and does not transfer to outcomes of interest.

In conclusion, even though there are many potential sources of error in our conceptualization and measurement of core psychological constructs, we believe that awareness regarding their presence as well as the implementation of procedural and statistical methods of control can serve to minimize their deleterious impact on research practices, and ultimately lead to more accurate inferences. Although this subsection does not provide an exhaustive account of such problems, it is meant to motivate researchers in this area to think deeply about the psychological constructs they study, and ways to optimize their measurement.

4.5 DEFINING THE 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 performance enhancement, 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 (Agar, 2013). 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 (Teichner, 1954). For example, a visual stimulus (e.g., 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 (Henderson & Dittrich, 1998; Wickens, 1974), 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 (Takemura et al., 2020). 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 (Cantello et al., 2000). 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 (Sugawara et al. 2013). 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 (Teichner & Krebs, 1974)). Classic reviews of simple reaction times find similar results, averaging about 220 milliseconds (Laming, 1968). 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 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 (Woods et al., 2015). Others have used windows of 100-1000 (Kida et al., 2005; Langner et al., 2010a,b), 100-500 (Forster et al., 2002), or only a lower limit of 150 ms (Miller & Low, 2001). 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 (Egoyan & Khipashvili, 2017). 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 (Forster et al., 2002). Multisensory inputs are even faster than single modalities, a phenomenon referred to as redundancy gain (Miller, 1982). Thus, even for the seemingly most basic of human behaviours, 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.

4.6 LONG-TERM EFFECTS OF NEUROSTIMULATION

Few studies within the enhancement literature have thoroughly examined potential long-term effects related to neurostimulation. Traditionally, the behavioural effects of neurostimulation are believed to be reversible and last up to approximately one hour (Nitsche et al., 2007). More recent studies have evaluated maintenance effects at longer post-stimulation intervals. For example, Au et al. (2021) conducted a study that combined the application of tDCS with working memory training. The application of tDCS occurred across six training sessions, with follow-up completed 1-month post-study. Only working memory performance was evaluated during the follow-up period, with no effects remaining. Similarly, Bjekić et al. (2019) and Vulić et al. (2021), each conducted studies where follow-up was completed 1-day and 5-days post-stimulation. Bjekić et al. (2019) examined the use of single session tDCS in improving face-word associative memory. Their follow-up only included an evaluation of the retainment of enhancements effects, where they found the effects persisted at the 5-day mark. Vulić et al. (2021) also evaluated enhancement of associative memory but included standard tDCS and tDCS oscillating in theta rhythm. In their follow-up periods they found that only the improvement of standard tDCS remained at the 5-day follow-up period. The lack of enhancement studies evaluating follow-on effects outside of duration of the enhancement is likely due to the majority of these studies using single session tDCS. Indeed, a recent systematic review on the topic of neurostimulation for enhancement purposes examining articles published between 2018 and 2022 (D'Alessandro et al., 2023) identified only two studies where neurostimulation was applied across multiple sessions out of the 97 total reviewed. Notably, neither of these studies included any sort of follow-up evaluation for duration of enhancement effects or associated side effects (tDCS, Bystad et al., 2020; multiple types of neurostimulation, Brem et al., 2018).

Regarding clinical applications of neurostimulation, there is more documentation available regarding some of the long-term considerations of its use. For example, Montenegro and Kissoon (2023) completed a review of the effects of long-term application of occipital nerve stimulation for the treatment of chronic migraines and cluster headaches. They report that overall, for the majority (≥50%) of patients in the included studies, the positive effects of the stimulation continued beyond 24 months. However, within this review, they also identified two studies where habituation, or a loss of efficacy, occurred (Leone et al., 2017; Leplus et al., 2021).

The literature examining clinical applications of neurostimulation has also evaluated tolerability of repeated applications of neurostimulation for treatment purposes. Recently, Pilloni et al. (2022) reported on the tolerability of repeated tDCS use that included 10 to 60 daily applications in six clinical trials. Their review concluded that repeated use of tDCS is tolerable across a range of individuals, and notably, its repeated use did not appear to increase the risk of adverse events, including risks such as skin lesions. However, one limitation of this study that is relevant to a military population, is that they did not evaluate whether there were changes to any non-targeted cognitive functions. Nor did they report on any changes to brain structure with the repeated application. While the lack of adverse events is promising, it remains unknown how the “healthy” brain may respond to similar repeated applications.

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Chapter 5 – FUTURE DIRECTIONS IN COGNITIVE NEUROENHANCEMENT

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5.1 BACKGROUND

This chapter provides an overview of future directions for cognitive neuroenhancement research and development, and several important considerations regarding the development and application of cognitive neuroenhancement techniques in military settings. One key area of focus is the need for improved mechanistic models and software tools. Existing models of neuroenhancement, such as non-invasive brain stimulation and neurofeedback, are limited in their ability to capture the complex interactions between neurons, electric field potentials, neural circuits, and behavioural outcomes. We highlight the importance of developing newer and more comprehensive models that can better inform the use of neuroenhancement techniques.

Additionally, this chapter explores the concepts of "addition by subtraction" and "subtraction by addition" in neuroenhancement, which suggest that reducing activity in certain brain regions or indirectly modulating functionally connected regions could lead to performance gains. The potential risks and challenges associated with these techniques, including the possibility of neurodiminishment and the need for biosensing technologies, are also discussed.

5.2 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 behavioural outcomes (Batsikadze et al., 2013; Monte-Silva et al., 2013), and has been repeatedly falsified through modelling and empirical work. For example, neuronal orientation relative to an induced electric field can differentially produce depolarization versus hyperpolarization of neuronal membranes (Dmochowski et al., 2012; Tranchina & Nicholson, 1986). The same challenges arise when considering polarity influences on neurons with varied morphology and function (Bonaiuto & Bestmann, 2015). 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.

Emerging mechanistic models instead focus on increasing evidence for non-linearity in the effects of neuroenhancement methods on brain activity and behaviour (Batsikadze et al., 2013; Bonaiuto & Bestmann, 2015). Specifically, while traditional models assumed that increasing the intensity and duration of tES would cause correspondingly increased intensities of activation or deactivation, more recent research suggests slightly different patterns. For example, Batsikadze administered 1mA versus 2mA cathodal tDCS to the motor cortex and measured motor cortex excitability (Batsikadze et al., 2013). They found 1mA to reduce motor cortical excitability, whereas 2mA increased it. Miniussi and colleagues discuss another phenomenon whereby introducing stochastic noise into simulations of brain function produces beneficial or detrimental effects as a function of its intensity (Miniussi et al., 2013). Adding to the complexity, when comparing 1mA to 2mA anodal tDCS over the left PFC, there is evidence that 1mA stimulation produces faster and more pronounced effects on behavioural outcomes than 2mA (Hoy et al., 2013). Similar results have been found when manipulating stimulation duration, with initially lower but then increased and prolonged effects of motor cortex tDCS with repeated stimulation (Liebetanz et al., 2006; Monte-Silva et al., 2013).

The possibility that brain stimulation, including at least TMS (Lackmy-Vallee et al., 2012) and tES (Bonaiuto & Bestmann, 2015), can induce non-linear effects on brain and behaviour, 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 (Bikson et al., 2012). Non-linear models, such as the ones using neural network attractor models (Bonaiuto & Bestmann, 2015), 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 behaviour.

Once more robust and validated mechanistic models of neuroenhancement effects on brain and behaviour 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 behaviour 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.

5.3 ADDITION BY SUBTRACTION

One emerging but under-researched theory of how neuroenhancement may induce effects is through addition-by-subtraction (Luber & Lisanby, 2014). 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 (Walsh et al., 1998). 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 (Alford et al., 2007), studies examining the reduction of cross-hemispheric inhibition (Hilgetag et al., 2001; Thut et al., 2005), and a study showing reduced costs of incongruent Stroop trials with rTMS targeting the anterior cingulate cortex (ACC) (Hayward et al., 2004). A more complete tabulation of TMS studies suggesting feasibility of an addition-by-subtraction mechanism can be found in the original theoretical position paper (Luber & Lisanby, 2014).

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 (Brunyé, 2018; Brunyé et al., 2019).

5.4 SUBTRACTION BY ADDITION

From a scientific perspective, as we continue to research neuroenhancement in academic and the defence 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.

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 Warfighters. Two critical considerations are important to note, in this vein:

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 where devices are becoming increasingly portable, untethered, and remotely controlled. While current technologies require Warfighters to wear devices on or around 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 Warfighters, and at a more refined level, such approaches could selectively alter brain activity and behaviour 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 targeted individual. 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.

5.5 BIOSENSING

Biosensing can provide insight into a Warfighter's physiological and neurological state - including stress levels, readiness, and disease state - by monitoring biomarkers, electrolytes, xenobiotics and other dissolved bioanalytes. Historically, high fidelity biosensing has been focused on blood collection which required invasive, bulky, specialized techniques within a medical office or laboratory. New advancements in the field of portable and wearable biosensors including the development of new sensing modalities, transduction mechanisms, and supporting power/communication electronics allow for non-invasive, continuous interrogation of previously underexplored biofluids including sweat, tears, saliva, or interstitial fluid (ISF) (Heikenfeld et al., 2019; Zhao et al., 2019). Researchers are actively working to develop sensors that are low-profile and flexible, and thus able to be seamlessly integrated into existing gear and lifestyle. Ultimately, migration from static, intermittent collection of the physiological state of military personnel to continuous monitoring platforms enables more complete knowledge of the interplay between physical state and biomarkers, and how they present in different biofluids. As the field continues to develop sensor technology, and learn from this data collected, the impact on health and medicine will continue to increase. As everyone has a unique profile, customized high-resolution monitoring with wearable systems can enable rapid diagnosis and assessment, allowing for personalized training or care (Tyler et al., 2020). This section discusses different accessible biofluids and biosensors and is particularly focused on biosensors designed to be worn for continuous physiological monitoring, due to the cognitive performance variability known to occur through the day in individuals. The components of the biosensors (the biorecognition element, the transduction mechanisms, and the signal readout) are not fluid or form factor specific and will be discussed throughout. This section will discuss the current state of the possible with respect to sensing different accessible biofluids. Emphasis is placed on biosensors with form factors that are amenable to continuous monitoring. Often, different sensors are targeting the same key biomarkers, but there is utility in being able to do take measurements in several different ways, and pros and cons associated with different sensing strategies.

5.5.1 Sweat-based Sensors

Sweat-based sensors are currently the most common wearable biosensor. The achievements and challenges associated with real-time sensing of analytes in sweat within wearable platforms has been recently reviewed

(Bariya et al., 2018; Brothers et al., 2019; Chung et al., 2019; Mohan et al., 2020). Sweat is an extremely accessible bodily fluid compatible with non-invasive, easy-to-wear sensors. Early prototypes of sweat-based sensors have been used to detect readiness, stress levels, or disease states, and monitor physical activity by collecting the dynamic biochemical profile of the wearer (Seshadri et al., 2019b). While traditional biomarker assessment has been completed via blood draws, eccrine sweat is proving to be information-rich, containing electrolytes, metabolites, amino acids, proteins, hormones, heavy metals (Gao et al., 2016) and other biomarkers (Emaminejad et al., 2017). These targets can be collected on a variety of wearable platforms, leveraging unconventional form factors and materials in unique body-interfaced sensors. There exist battery-free soft colorimetric microfluidic systems integrated on the skin (Bandodkar et al., 2019; Choi et al., 2019; Koh et al., 2016), designed to detect electrolytes, metabolites (such as glucose and lactate), pH, sweat volume, and temperature. Other demonstrations include multi-target sensor arrays with integrated wireless data transmission that are battery powered (Currano et al., 2018; Gao et al., 2016) and human-powered (triboelectric powered with Bluetooth capabilities) (Y. Song et al., 2020). Motivated by the high density of sweat glands in the hands, researchers have demonstrated gloves with integrated electrochemical sweat sensors (Bariya et al., 2020), allowing for detection of electrolytes, xenobiotics, alcohol, zinc, chloride, and pH and vitamin C. Custom wicking architectures have been developed for electrochemical sweat sensors (Y. Yang et al., 2020) designed to detect uric acid and tyrosine.

Two important analytes of interest for non-invasive sensing platforms with implications in neuroenhancement are glucose and cortisol (Emaminejad et al., 2017, 2017; J. Kim et al., 2018). Metabolites such as glucose provide energy for the brain, which accounts for up to 20% of the body's total consumption (Jha & Morrison, 2018; Magistretti & Allaman, 2015). Enzymatic glucose sensing often acts a model system for the development sensor platforms for various biomarkers, leading to multiple demonstrations of early and advanced glucose sensor prototypes (Welch et al., 2015) that can be modified to sense a wider range of biomarkers such as adrenalin and lactate acid. Cortisol sensing is of significant interest as an indicator for stress and readiness. The active form of cortisol has been found in the set of non-invasive bodily fluids discussed here, including sweat, and thus is amenable to wearable sensors. Wearable cortisol sensing platforms have been recently reviewed (Upasham, Churcher, et al., 2021)02/08/2023 10:05:00. For the development of electrochemical cortisol sensors, researchers are exploring the use of receptor molecules including antibodies, enzyme fragments, molecularly imprinted polymers (Parlak et al., 2018), and other biomimetic materials. Researchers have demonstrated a sweat-based circadian diagnostic platform to map chronobiology by sensing cortisol and Dehydroepiandrosterone (DHEA) (Upasham, Churcher, et al., 2021; Upasham, Osborne, et al., 2021). Cortisol sensors based on single stranded Deoxyribonucleic acid (DNA) aptamers have been used to monitor circadian tracking of cortisol in real time (Ganguly et al., 2021). It is worth highlighting this unique recognition element: aptamers are essentially "chemical antibodies" that are stable at room temperatures and across broad range of working conditions. These engineered chemicals provide a quantitative, rapid response and can be precisely optimized to capture biomarkers of interest on a wearable platform. While there are documented cons associated with aptamers as biorecognition elements, including possible nuclease degradation and high cross reactivity (Lakhin et al., 2013), aptamer-based biosensors are showing great promise for continuous drug monitoring and cortisol sensing (Fernandez et al., 2017) via wearable sensors (Bian et al., 2021).

Overall, sweat-based sensing is showing great promise for providing the ability to continuously track physiological and neurological state. Significant challenges remain, including low sample volumes (nano to microliter), variable concentration due to evaporation, filtration and dilution of large analytes, and contamination with skin (including environmental factors and old sweat.)[1] Further advances related to both the sensing technology (i.e. sensitivity, specify, power and communication) and backend data analysis (anomaly detection and disease state identification) will render sweat sensing and increasingly important strategy for performance monitoring.

5.5.2 Interstitial Fluid Sensors

Interstitial fluid (ISF) sensors may overcome some of the challenges associated with sweat sensors. ISF refers to the fluid surrounding cells. It is a particularly rich source of soluble bioanalytes including proteins, peptides, metabolites, and nucleic acids (Heikenfeld et al., 2019; Müller et al., 2012; Tran et al., 2018). ISF exhibits similar proteomic and transcriptomic profiles as blood, and even exhibits biomarkers not found in blood that are associated with local cellular processes.

While there exist multiple invasive methods for assessing ISF (Madden et al., 2020), their practical use is limited. Microneedles, solid or hollow needles that are less than 1 mm in length, may allow for the minimally invasive the collection of ISF. Microneedles pierce the epidermis, essentially creating transient pores in the skin to allow transport of large polar molecules across the skin, painless to the wearer. Various strategies exist for integrating the sensor component with microneedles. The chemistry is similar to the immunoassays and electrochemical sensing employed in sweat sensors, with form factor adapted to microneedle geometry. The field of wearable microneedles is still in its infancy. While there are some commercial demonstrations of transdermal delivery, there are no commercial devices for transdermal extraction or sensing, but some successful research demonstrations (Y. Kim & Prausnitz, 2021).

Microneedles fabricated and modified with electrochemical biosensor surfaces have demonstrated detection of transdermal alcohol (Venugopal et al., 2008) and other pharmaceuticals (Goud et al., 2019). Hollow microneedles have been combined with ion-selective electrodes (ISE) for potassium detection, which is useful metric to track during exercise, or use an indicator for disease and organ failure (Miller et al., 2014). There are also multiple examples of sensing glucose levels in ISF via microneedles (K. B. Kim et al., 2019; Madden et al., 2020). Miller et al. conducted important studies comparing ISF collected with microneedles and blood. For their device, they used modified commercially available glass pipettes as the microneedle, and collected tens of microliters from individuals over approximately 10 mins. Proteome and transcriptome analysis demonstrated the similarities between ISF, serum and plasma (Miller et al., 2018). Recently, research has demonstrated extremely sensitive sensing of biomarkers in ISF via microneedle-integrated immunoassay coupled with an ultrasensitive fluorescent label. In this demonstration, the microneedle patch, decorated with capture probes for the analyte of choice. After a few minutes, the patch was removed, and on needle analysis and detection employed an antibody and an ultrabright label (plasmonic-fluor nanostructure) (Wang et al., 2021). They used their microneedle patch to monitor the efficiency of a cocaine vaccine as well as inflammatory biomarker levels.

As with the field of sweat sensing, microneedle based ISF sensing also faces many challenges. In recent years, significant advances have been in microneedle sensor fabrication, allowing for better collection and assessment of ISF. More tools to characterize ISF will allow for a better understanding of the relationships between biomarkers and xenobiotics in ISF and physiological and neurological state.

Saliva is also an information-rich biofluid containing various biomarkers that reflect both normal and disease state, and potential give insight into cognitive and neurological function. The field of saliva-based biosensors has been recently reviewed (Malon et al., 2014; Ilea et al., 2019). Researchers have demonstrated saliva-based biosensors that detect glucose, lactate, cortisol, and proteins (M.-H. Lee et al., 2011) associated with cancer, tobacco use and cardiovascular disease. The mouth also has a rich oral microbiome, and sensors have been developed to detect specific bacteria (Ahmed et al., 2013) associated with disease state, as well as antibodies (Zaitouna et al., 2015). Smartphone-based portable saliva sensors to detect glucose have been demonstrated (Soni & Jha, 2017), using cloth-based sensors provided to the subject to collect saliva samples. Such sensing strategies could be excellent for highly portable sensing in a field-forward location, which often do not lend itself very well to wearable sensing. Recently, researchers demonstrated a low-profile mouthguard with integrated glucose sensor and wireless transmitter (Arakawa et al., 2020). In this demonstration, the glucose sensing element was modified with a cellulose acetate membrane that serves as an interference rejection membrane, improving sensor selectivity and allowing glucose detection in non-pretreated saliva. This form factor and interference strategy could be adapted for other analytes related to changes in cognitive states, such as cortisol or xenobiotics.

5.5.3 Saliva-based Sensors

Saliva is extremely information rich and can be an attractive diagnostic fluid, but associated challenges, such as the complexity of the fluid, including the presence of digestive enzymes and the comfort of a continuous monitoring device, limit current widespread utility in wearable sensing. Advances in selectivity strategies and device electronics could improve the pace of technology adoption.

5.5.4 Tear-based Sensors

Tears are another minimally invasive, information-rich bodily fluid. Sensors within a contact lens form factor that monitor physiological parameters (J. Kim et al., 2017) have been developed and demonstrated. Researchers have shown that commercial contact lenses (CL) can serve as sample collectors for subsequent analysis of analytes of interest (Ballard et al., 2020). In this study, they found lysozyme non-specifically bound to the CL material. Monitoring lysozyme concentration can provide immediate insight into patient eye health. The technique could be expanded to support multiplexed detection of a panel of tear biomarkers for broader diagnostics applications. Using laser-inscription, microfluidic contact lenses were developed as wearable platforms for *in situ* tear pH, glucose, protein, and nitrate sensing. Smartphone-enabled colorimetric readouts provided analyte concentration. This simple device may have utility in ocular health monitoring, but does not lend itself equally well to continuous, digital monitoring (Moreddu et al., 2020) for use in field-based performance measurements. Wireless smart contact lenses that allow for glucose monitoring and controlled drug delivery have been recently demonstrated. Flexible circuitry is integrated within a biocompatible polymer and CL form factor (Keum et al., 2020). The closed-loop sensing and treatment cycle could be adapted to multiple sensing and triggering processes. Similarly, flexible graphene field effect transistors have been incorporated into a CL form factor for sensing cortisol in tears (Ku et al., 2020). Transparent antennas and wireless communication circuits allow data exfiltration. This work has been has successfully demonstrated in both an animal model and humans. Continued advances in device fabrication make CL-based sensing a promising area for both physiological and cognitive performance monitoring. non-invasive subcortical targets

5.6 MULTIMODAL NEUROENHANCEMENT

Multiple neuroenhancement approaches used simultaneously or in succession have the potential to provide greater value for enhancing human performance compared to a single neuroenhancement approach. This is primarily because different neuroenhancement techniques target distinct neural mechanisms and cognitive processes, allowing for a broader range of improvements and potentially synergistic effects. By combining multiple approaches, researchers can explore whether the effects are additive, subtractive, or interact in other interesting ways.

One reason why multiple neuroenhancement approaches may be valuable is that each technique typically focuses on enhancing a specific aspect of cognition or brain function. For example, one approach might aim to improve memory retention, while another might enhance attention or problem-solving abilities. By using these techniques in conjunction, individuals could potentially experience improvements in multiple cognitive domains simultaneously, leading to a more comprehensive enhancement of overall performance.

Furthermore, combining different neuroenhancement approaches could result in interactive effects, where the combination produces a greater impact than the sum of its individual components. This could occur through various mechanisms, such as complementary actions on neural pathways or synergistic effects on neurotransmitter systems. For instance, a cognitive training program that enhances working memory might synergistically amplify the benefits of a pharmacological intervention or electrical neurostimulation intervention designed to enhance focus and attention (see Ward et al., 2017 and Weller et al., 2020 for examples of such possibilities).

Exploring the additive, subtractive, or interactive effects of combining multiple neuroenhancement approaches could be a promising direction for future research (Brunyé et al., 2020; Steinberg et al., 2019). By systematically investigating different combinations and sequences of techniques, researchers could identify optimal approaches for enhancing specific cognitive functions or achieving desired outcomes. Additionally, understanding the interactive effects may uncover novel insights into the underlying neural mechanisms and provide a basis for developing more effective and tailored neuroenhancement interventions.

However, it is important to approach this research with caution and ethical considerations. Potential risks and unintended consequences need to be thoroughly evaluated, as interactions between different neuroenhancement techniques may have unforeseen negative effects or long-term consequences. Proper regulatory frameworks and guidelines should be established to ensure responsible and safe use of these approaches in enhancing human performance.

5.7 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 (Stanslaski et al., 2012; Sun & Morrell, 2014). 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 (Choi et al., 2020; Ketz et al., 2018). 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 (Zhang & Gruber, 2019). 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 (G. Li & Chung, 2018), 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 (McKinley et al., 2012; Silvanto et al., 2008). Change point estimation is a challenging modelling problem, especially when considering brain dynamics that will likely have very low signal to noise ratios in real-world environments (Zhou et al., 2018). Second, closed-loop neuroenhancement requires high fidelity targeting of brain regions that are reliably linked to modulating relevant task outcomes (Nitsche et al., 2019).

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 behaviour (Bastani & Jaberzadeh, 2014; Behrens et al., 2017; Jamil et al., 2017; Nitsche & Paulus, 2001), and that repetitive neurostimulation can sometimes produce paradoxical effects (Monte-Silva et al., 2010), the potential influences of repeatedly and briefly triggering stimulation need to be better elucidated.

Chapter 5 – REFERENCES

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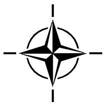

Chapter 6 – SUMMARY RECOMMENDATIONS FOR COGNITIVE NEUROENHANCEMENT RESEARCH AND DEVELOPMENT

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6.1 BACKGROUND

Throughout this report, the group has identified and described several important considerations for the development and application of cognitive neuroenhancement techniques in military settings. This chapter summarizes the most critical recommendations for continuing research and development on cognitive neuroenhancement.

6.2 DEVELOP MODELS TO PREDICT THE EFFECTS OF NEUROSTIMULATION INTERVENTIONS

Currently, there is no guidance to customize parameters as a function of the individual, context, or task, while for example different individuals can show varied and non-linear effects of stimulation. Current mechanistic models of neurostimulation effects on brain and behaviour do not afford any such customization.

6.3 DEVELOP MORE COMPREHENSIVE AND VALIDATED CURRENT PROPAGATION MODELS

Simple models such as “anodal electrical stimulation results in excitation, and cathodal in inhibition” have been repeatedly falsified, yet scientists continue to rely on such outdated models. The field needs biologically plausible models that can guide validation efforts with optimized stimulation protocols. These models should take into account current propagation (including cranial structure and composition) and low-level interactions between propagating energy and neurobiological structures (within neural populations and at the cellular and sub-cellular scales).

6.4 DEVELOP BRAIN MODELS TO ENHANCE MECHANISTIC UNDERSTANDINGS

The models of signal propagation described above could be integrated with biophysically realistic neuron models and computational cognitive models to make predictions about how neurostimulation alters cognitive functions. The research community lacks a generally accepted mechanistic theory to account for neuroenhancement effects on brain and behaviour. Proposed mechanisms include neuroplastic alterations of white matter and myelination, activating intrinsic homeostasis and self-organization of the brain, and altering network functional connectivity. The latter is of great relevance.

6.5 DEVELOP DEEPER UNDERSTANDING OF THE TARGETED CONSTRUCTS

Typically, neuromodulation approaches are motivated by resource models of cognition, according to which specific abilities and/or capacities are conceptualized to represent a limited resource (e.g., working memory). This theoretical approach suggests that the specific ability and/or capacity exists in limited supply, and that enhancement via neuromodulation is expected to lead to an increase in the underlying resource. However, fundamentally, it has proven difficult to associate changes in cognitive performance to increases (or decreases) in the underlying construct that is the target of the intervention. In addition, similar problems exist in interpreting intervention-related changes in neural function to variation in the targeted resource (e.g., working memory). It is essential that one develops a better understanding of the targeted constructs in order to have an accurate representation of how the intervention is enacted within the brain and reflected in behaviour.

6.6 DEVELOP A NETWORK-BASED, HOLISTIC APPROACH TO NEUROENHANCEMENT

The zero-sum model suggests that stimulation causes a net zero-sum gain through antagonistic modulation of various brain regions: activation in the targeted region may co-occur with de-activation in another region or part of the network. At this point, it is unknown how any net zero-sum effects will be realized at the macro-level or micro-level.

Studies that examine the effects of neuroenhancement approaches within a single domain may be overestimating the extent to which any enhancement can be achieved in more realistic contexts that demand more diverse central processing. 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. This includes studying the (beneficial) effects of deactivating effect, or how reducing activity in brain regions that compete with a process of interest can lead to performance gains, also known as addition by subtraction.

6.7 CHARACTERIZE ADDITION-BY-SUBTRACTION EFFECTS

Targeting a specific structure cannot be done without taking into consideration the possible effects of this intervention on the network within which it resides, as well as the other networks that it is functionally connected to. For example, downregulating inhibitory regions could prove advantageous to task performance. Another application of downregulation of brain areas is neurodiminishment (negatively influence performance) which is hardly studied but might be advantageous in some scenarios and from a military perspective.

6.8 STUDY NEURODIMINISHING EFFECTS

Neurodiminishment might be relevant in military scenarios. For example, impairing executive function can improve the effectiveness of interrogation, impairing memory consolidation can reduce the likelihood of developing a stress disorder, or shutting down rumination under stress can improve sleep quality. However, neurodiminishment could also be used in the opposite manner by adversaries to directly exert power and influence over our Warfighters. Two critical considerations are important to note, in this vein: neuroenhancement technologies will likely become a target for electronic warfare, and future technologies will very likely be able to induce neurodiminishing effects using stand-off directed energy sources.

6.9 DEVELOP METHODS TO TARGET DEEP BRAIN STRUCTURES

Established neurostimulation techniques are relatively limited in their depth. No research to date has assessed how subcortical stimulation affects human performance, while altering activity in distant regions is an interesting and relevant topic in neuroenhancement. An approach could be to focus on superficial neuroenhancement method such as tDCS or tACS to indirectly modulate functionally connected subcortical regions.

6.10 STUDY THE EFFECTS OF COMBINED INTERVENTIONS

Many neuroenhancement techniques are considered in isolation, while recent reviews suggest utility in summarizing converging evidence across neuroenhancement modalities. Multiple neuroenhancement approaches used simultaneously or in succession have the potential to provide greater value for enhancing human performance compared to a single neuroenhancement approach. Exploring the additive, subtractive, or interactive effects of combining multiple neuroenhancement approaches is a promising direction for future research. Combining neurostimulation with other enhancement interventions, such as pharmaceuticals, exercise and cognitive training, is also a relevant yet under-researched topic.

6.11 INVESTIGATE EFFECTS OF PROLONGED AND REPEATED USAGE

Studies incorporating prolonged effects are limited. This holds both for prolonged effect of the performance enhancement itself as well as for long-term safety and sensitization profiles. 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.

6.12 INVESTIGATE INDIVIDUAL DIFFERENCES, TRAITS, AND STATES

Individual differences affect the outcomes of neuromodulation techniques. Known factors include for instance difference in expertise and motivation, but systematic knowledge on how individual differences, traits and states can account for effectiveness of performance enhancement is lacking. Relevant aspects include neurochemical and neurophysiological differences, skull thickness, sex and gender, and transient states like stress, emotional state, physical exertion, sleep, dehydration, thermal load, and nutritional deprivation. Once the relevant states are identified, closed-loop neuroenhancement systems can be developed.

6.13 DEVELOP SENSE AND CONTROL ALGORITHMS FOR CLOSED-LOOP NEUROENHANCEMENT

By combining neural sensing, machine learning (linking sensor data to expected performance), and neurostimulation modalities, closed-loop neuroenhancement devices can dynamically modulate stimulation parameters as a function of sensed and inferred mental and/or physical states. Closed-loop neuroenhancement techniques have also begun to receive attention in the domain of human performance enhancement but require sensitive and specific sensing and high fidelity targeting.

6.14 TRANSLATE LABORATORY FINDINGS TO FIELD ENVIRONMENTS

Moving neuromodulatory enhancement techniques from the laboratory to the field is a critical component for the realization of these techniques for the Warfighter. However, to date, little such research exists. Some applications may still need a controlled environment, such as TMS devices with limited portability, and can be most suitable for military educational and training contexts. Other techniques are potentially applicable in field operation, and we should start collecting the necessary evidence that the technology is ready to transition to applied settings for military use.

6.15 SURVEY AND MITIGATE ADVERSE SIDE EFFECTS

Experimental and meta-analytic research have demonstrated varied side effects and adverse events associated with different neuroenhancement techniques. As consumer-grade transcranial and transcutaneous electrical stimulation devices continue to proliferate the market, it is likely that the home-use of these devices will lead to a rise of reported adverse side effects. From both safety and user acceptance perspectives, adverse side effects should be surveyed, and mitigation approaches must be investigated. Safety is one of the key aspects along with other ethical considerations.

6.16 INCLUDE ETHICS AND SAFETY IN RESEARCH AND DEVELOPMENT

It is important to approach neuroenhancement research with caution and ethical considerations. Proper regulatory frameworks and guidelines should be established to ensure responsible and safe use of these approaches in enhancing human performance. 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. 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. There is also a gap in regulatory oversight of neuroenhancement techniques and a comprehensive framework to understand and model the ethics of neuroenhancement can inform regulation in this domain.

6.17 DEVELOP STANDARDIZED PROTOCOLS WHERE POSSIBLE

Each neuroenhancement technique has myriad parameters that are often selected and manipulated inconsistently or without ample justification. In addition, experimental methodologies are highly varied and may underlie disparate effects on cognitive performance. These limitations make it difficult to derive consistent or compelling insights from the extant literature. Where possible, standard intervention protocols and minimum reporting standards should be established, including technical characteristics of the device, stimulation parameters applied, and methodological considerations (inclusion/exclusion criteria, outcomes, side effects) to ensure adequate reporting and reproducibility. For the neuroenhancement field to proceed efficiently, standardized protocols will help solve methodological weaknesses that pervade the scientific literature.

6.18 OVERCOME COMMON METHODOLOGICAL WEAKNESSES

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. Other potential weaknesses include: a) outcome tasks: it is important to obtain performance measurements representing a holistic view of human cognitive performance as compared to baseline performance on tasks in – at minimum – a realistic scenario and study the transfer to similar but unlearned tasks; b) sham: research should focus on developing more effective sham procedures to ensure adequate blinding; c) defining psychological constructs: researchers should think deeply about the psychological constructs they study, and ways to optimize their measurement; d) registered reports: neuroenhancement research would benefit from this mechanism that helps reducing the inherent disincentivizing of null or unexpected results and help and assigning equal value to manuscripts reporting null or counter-intuitive results assuming sample size criteria are met; e) use sample sizes that maximize power and minimize the likelihood of a Type I error.

6.19 CONCLUSION

In conclusion, neuroenhancement for military applications requires significant advancements in several areas of basic and applied research and development. To achieve personalized and optimized neurostimulation interventions, it is crucial to develop models that accurately predict the effects of such interventions, considering individual differences, context, and task. Simple and outdated models of signal propagation must be replaced with biologically plausible models that incorporate cranial structure, composition, and low-level interactions. Integrating these models with biophysically realistic neuronal models and computational cognitive models can enhance our understanding of how neurostimulation affects cognitive and potentially physical functions.

Furthermore, a network-based approach to neuroenhancement is necessary, considering the prevalence and relevance of unanticipated effects including net zero-sum and addition by subtraction. Exploring the effects of combining interventions and targeting deep brain structures should also be pursued. It is essential to investigate prolonged effects and usage, individual differences, traits, and states, and develop closed-loop neuroenhancement systems.

Finally, moving beyond laboratory environments and surveying and mitigating adverse side effects are critical steps. Ethics, safety, and standard protocols must be developed and incorporated into research and development, and common methodological weaknesses need to be resolved. By addressing these areas, we can pave the way for responsible and effective neuroenhancement techniques in military contexts while prioritizing the well-being and autonomy of individuals. A final summary table detailing the safety, maturity, and FDA approval for various neuroenhancement technologies can be found in Table X.

Table 9: The Safety, Maturity, and FDA Approval Status of Neuroenhancement Technologies.

Technology	Safety	Maturity	FDA approval*
TMS	🟩	🟨	Yes
tES	🟩	🟨	No
tFUS	🟨	🟨	Yes
TPNS	🟨	🟨	Yes**
CES	🟩	🟨	Yes
PBM			
NF	🟩	🟩	Yes

🟩 = Strong evidence
🟨 = Mixed evidence
🟥 = Weak evidence

TMS = transcranial magnetic stimulation; tES = transcranial electrical stimulation; tFUS = transcranial focused ultrasound stimulation; TPNS = transcutaneous peripheral nerve stimulation; CES = cranial electrotherapy stimulation; PBM = photobiomodulation; NF = neurofeedback.

* FDA approval can apply to a multitude of conditions (e.g., clinical diagnostic criteria such as major depressive disorder [MDD], etc.) that may not necessarily be linked to cognitive neuroenhancement.

** This approval applies to *percutaneous* (i.e., penetrating non-intact skin) peripheral nerve stimulation. See Beltran-Alacreu et al., 2022 for a description of differences between percutaneous and transcutaneous formats.