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STO TECHNICAL REPORT **TR-HFM-311**

Neuroenhancement in Military Personnel: Conceptual and Methodological Promises and Challenges

(Neuro-amélioration du personnel militaire : promesses et défis conceptuels et méthodologiques)

Final report of Research Task Group HFM-311.

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Science & Technology (S&T) in the NATO context is defined as the selective and rigorous generation and application of state-of-the-art, validated knowledge for defence and security purposes. S&T activities embrace scientific research, technology development, transition, application and field-testing, experimentation and a range of related scientific activities that include systems engineering, operational research and analysis, synthesis, integration and validation of knowledge derived through the scientific method.

In NATO, S&T is addressed using different business models, namely a collaborative business model where NATO provides a forum where NATO Nations and partner Nations elect to use their national resources to define, conduct and promote cooperative research and information exchange, and secondly an in-house delivery business model where S&T activities are conducted in a NATO dedicated executive body, having its own personnel, capabilities and infrastructure.

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The total spectrum of this collaborative effort is addressed by six Technical Panels who manage a wide range of scientific research activities, a Group specialising in modelling and simulation, plus a Committee dedicated to supporting the information management needs of the organization.

- AVT Applied Vehicle Technology Panel
- HFM Human Factors and Medicine Panel
- IST Information Systems Technology Panel
- NMSG NATO Modelling and Simulation Group
- SAS System Analysis and Studies Panel
- SCI Systems Concepts and Integration Panel
- SET Sensors and Electronics Technology Panel

These Panels and Group are the power-house of the collaborative model and are made up of national representatives as well as recognised world-class scientists, engineers and information specialists. In addition to providing critical technical oversight, they also provide a communication link to military users and other NATO bodies.

The scientific and technological work is carried out by Technical Teams, created under one or more of these eight bodies, for specific research activities which have a defined duration. These research activities can take a variety of forms, including Task Groups, Workshops, Symposia, Specialists' Meetings, Lecture Series and Technical Courses.

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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 behavior 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 behavior. 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 with 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 behavior.

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 a 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 differences 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 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; and

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 6-1.

Table 6-1: 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.)**

6.20 REFERENCES

Beltran-Alacreu, H., Serrano-Muñoz, D., Martín-Caro Álvarez, D., Fernández-Pérez, J. J., Gómez-Soriano, J., and Avendaño-Coy, J. (2022). Percutaneous versus transcutaneous electrical nerve stimulation for the treatment of musculoskeletal pain. A systematic review and meta-analysis. Pain Medicine, 23(8), 1387-1400.