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Interim Recommendations for Cognitive Enhancers for FVL Operators and Aircrew: A Summary Report

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14. ABSTRACT

The U.S. Army's rotary-wing aircraft modernization effort, Future Vertical Lift (FVL), promises aircraft that exceed the performance parameters of the current fleet with respect to faster speeds, increased maneuverability and precision, and capacity to facilitate longer duration missions. These changes to the aircraft's design and capabilities will also translate into changes to the cognitive demands placed on aircrew. In order to promote mission success, evaluation of potential tools and techniques for cognitive enhancement and ultimately functional performance of operational tasks is needed. In this report, we summarize research findings and provide discussion of recommendations for the potential use of cognitive enhancers for FVL operators and aircrew.

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Introduction

The U.S. Army's rotary-wing aircraft modernization effort, Future Vertical Lift (FVL), promises aircraft that exceed the performance parameters of the current fleet with respect to faster speeds, increased maneuverability and precision, and capacity to facilitate longer duration missions. These changes to the aircraft's design and capabilities will also translate into changes to the cognitive demands placed on aircrew. In order to promote mission success, evaluation of potential tools and techniques for cognitive enhancement and ultimately functional performance of operational tasks is needed. In this report, we summarize research findings and provide discussion of recommendations for the potential use of cognitive enhancers for FVL operators and aircrew.

Technical Challenge 1: Review Literature on Use of Cognitive Enhancing Strategies in Operational Environments

A systematic review was conducted to identify and summarize the existing literature with respect to cognitive enhancement effects of tools including pharmaceuticals, transcranial electrical stimulation, herbal and vitamin supplements, training, sleep, aerobic exercise, and meditation (Kelley et al., 2019). The findings of this review support a number of cognitive enhancement interventions. However, the strength of that support varies and is affected by moderating variables as well as inconsistent results across the literature. The interventions with the strongest support are pharmaceuticals and transcranial electrical stimulation which may be a reflection of the amount of attention given to these interventions and not purely the strength of the interventions' effects. While the methodology used here complimented the study purpose, it is not exhaustive by any means and the results are thus limited to some degree. First, the methodology was not designed to identify novel or underrepresented interventions. Thus, we find that the interventions with the most support are also those with the most attention (pharmaceutical stimulants and transcranial electrical stimulation). Also, some interventions with potential for functional enhancement were not picked up using this approach. Additional research is needed prior to implementation of cognitive enhancement interventions in military settings, especially considering the unknowns associated with undesirable secondary and post-enhancement effects for these interventions.

Technical Challenge 2: Determine Efficacy of Pharmacological Countermeasures to Enhance FVL Aircrew Performance

The use of pharmaceuticals to restore performance under varied operational stressors as well as to enhance performance has been a highly debated topic in the military aviation community for many years. Presently, all services encourage the use of caffeine to counteract fatigue associated with insufficient rest or long duration missions. The U.S. Air Force and U.S. Navy both allow for and encourage modafinil use (over dextroamphetamine) to sustain vigilance or wakefulness (the U.S. Army's policy for allowing modafinil is in progress but has not yet been finalized). All services allow the use of dextroamphetamine but within strict guidelines that allow for use only when other fatigue countermeasure options have been exhausted.

The purpose of this report, however, is to evaluate the efficacy of pharmaceuticals for enhancement purposes rather than restoration of performance. Presently, the "off-label" use of modafinil and dextroamphetamine for performance enhancement is not allowed in military aviation. Yet, the possibility of such in the future is not obsolete. The systematic review described above identified a total of eleven drugs and drug classes for enhancement purposes. The most researched drug was modafinil with studies of doses ranging from 100-400 milligrams (mg). The most consistent finding is the moderating effect of baseline performance on enhancement such that enhancement properties were limited to low baseline performers. Considering the findings of this review alongside the findings of a 2015 systematic review specific to modafinil of studies published from 1990-2015, there appears to be consistent evidence in support of enhancement of low-level cognitive processes but not for higher-order processes or complex tasks (Battleday & Brem, 2015). There is some recent evidence in support of attention enhancement whereas past research findings have been mixed (Battleday & Brem, 2015; Repantis et al., 2010). The variability in tasks used to measure attention and its sub-component, alertness, may be a contributing factor to the mixed results that are also likely confounded by individual differences. The source of this inconsistency in findings is only speculated upon at this point and needs to be further examined prior to decisions regarding implementation in military settings. Importantly, the studies reviewed did not suggest any negative side effects or mood changes associated with modafinil, consistent with past findings (Battleday & Brem, 2015). The U.S. Army Aeromedical Research Laboratory (USAARL) conducted a head-to-head comparison of modafinil and mixed amphetamine salts for cognitive function enhancement. The functional tasks were not specific to aviation, however, the findings do have implications for aviators. The efficacy of modafinil to enhance performance was very limited and confounded by one's abstract reasoning ability. If we assume that aviators are above average abstract reasoners, then it is likely that modafinil efficacy at a low dose in this subpopulation will be extremely limited, if existent (Kelley et al., 2021). Taken together, modafinil may be useful for enhancement in some military settings given that it is not habit-forming, does not appear to yield any negative secondary effects, and does have considerable support suggesting some enhancement properties, however, limited.

Similar findings to those for modafinil were seen for amphetamine and mixed amphetamine salts (e.g., Adderall). Specifically, enhancement was moderated by baseline performance with enhancement limited to low baseline performers. The cognitive constructs enhanced included non-verbal convergent creative thinking, reasoning, and episodic memory whereas mixed results were seen for vigilance and verbal learning. No enhancement was found for divergent thinking, verbal creative thinking, working memory, or inhibitory control. In fact, one study suggested decremented working memory, processing speed, visual learning, and verbal learning performance in high baseline performers. Again, similar to modafinil, other reviews have found that mixed amphetamine salts may be appropriate for enhancing performance on simple tasks and sustained attention, yet inappropriate for performance on more complex tasks and selective attention given increases in impulsivity seen following administration (Advokat, 2010). In the USAARL's head-to-head comparison study, mixed amphetamine salts enhanced performance, however, some negative side effects were reported, and again the effect was moderated by abstract reasoning. Thus, the overall conclusion regarding mixed amphetamine salts is that there may be some enhancement potential although that potential is limited in scope and applicability. Additionally, mixed amphetamine salts are addictive and have potential for abuse, making them less attractive for implementation.

Methylphenidate is another potential drug for cognitive enhancement with mixed results in the literature and concerning negative secondary effects (as well as addictive properties). The review yielded evidence for enhancement of associative learning, error awareness, alertness, and visual perception processing speed with large effect sizes when reported. Doses ranged from 20-40 mg and some findings were moderated by baseline performance level with some enhancement limited to low performers and some limited to high performers. These findings are consistent with those from a published literature review of single-dose studies published between 1978 and 2013 showing evidence in support of working memory and processing speed enhancement (Linssen et al., 2014). Translation of any enhancement properties to complex tasks has not been established, however, and is needed prior to recommending consideration for military settings.

Donepezil, a central acetylcholinesterase inhibitor, which is prescribed typically to treat confusion in Alzheimer's patients, has also been shown to enhance procedural, verbal, visual, working, and spatial memory (Reches et al., 2014), information processing and some executive function for a single dose in healthy adults (see Repantis et al., 2010 and Fond et al., 2015 for reviews). Donepezil is thought to impact cognitive function by slowing the breakdown of acetylcholine, thus increasing cholinergic synaptic transmission in the brain, and extending its duration in the synaptic cleft (Broussard, 2012). Common side effects for continuous use include nausea, diarrhea, lethargy, dizziness, and insomnia (Dunn et al., 2000). Donepezil does not appear to be moderated by baseline abstract reasoning or cognitive function and is the focus of a current USAARL study.

Finally, the enhancement results for the other drugs and drug classes included in the review (selective serotonin reuptake inhibitors cholinesterase inhibitors, serotonin and norepinephrine reuptake inhibitors, nootropics, selective inhibitor of cyclic guanosine monophosphate, nicotine, and antibiotics) were mixed. Specifically, enhancement from escitalopram appears to be confounded by task familiarity in the study. Ceretrophin and physostigmine showed enhancement for abstract reasoning and visual attention, respectively. These drugs may be potentially useful in military settings; however, additional replication studies are needed.

Technical Challenges 3 & 4: Determine Efficacy of Transcranial Electrical Stimulation (TES) at Enhancing Performance in Laboratory/Low Fidelity Simulation and High Fidelity Simulation

In the systematic review described above, five forms of transcranial electrical stimulation were identified for enhancement purposes. These included transcranial direct current stimulation (tDCS) (33 studies), oscillating direct current stimulation (1 study), intermittent theta-burst stimulation (2 studies), transcranial alternating current stimulation (4 studies), and repetitive transcranial magnetic stimulation (rTMS) (6 studies including one combined with amoxetine). Among these five forms, the stimulation parameters used within studies varied greatly. However, in terms of outcomes, several consistent findings were seen. These were primarily enhancement of learning tasks, perception-based tasks, visuospatial attention, and recall tasks. The consistencies were found across the five forms of stimulation identified. These results partially align with past reviews of literature on this topic. For example, enhancement of learning has been found for motor learning. Specifically, one review that examined the effects of tDCS including only studies where the placement of the anode was over M1 determined that the effects

of stimulation on learning may depend on the stage of learning when stimulation is applied, as well as the tasks assessed and stimulation parameters used (Hashemirad et al., 2016). The variability of studies finding enhancement or none has been supported in other reviews. For example, a recent meta-analysis of tDCS effects on working memory concluded that the enhancement of working memory by application of tDCS still remained uncertain, but that application of anodal stimulation to the left dorsolateral prefrontal cortex (DLPFC) *during* working memory training appeared to have the greatest potential (Mancuso et al., 2016). Similarly, application of rTMS over the DLPFC was concluded to improve working memory in one review article, whereas application of tDCS only improved reaction time for working memory tasks (Brunoni & Vanderhasselt, 2014).

The USAARL conducted two studies of tDCS with promising results. The first study was not specific to aviation performance, however, did test Soldiers on both cognitive and operationally relevant tasks (e.g., marksmanship) (Feltman et al., 2021). The results showed that tDCS applied to the left DLPFC at 2 milliamps (mA) for 30 minutes during cognitive tasks, resulted in improved throughput on the marksmanship task. The method of tDCS application chosen for this study, where participants received tDCS prior to completing the military functional tasks, was done to better replicate what is currently (based on the available technology) a potential method for using tDCS in the field. Although we were able to demonstrate the transferability of the performance effects of tDCS from cognitive tasks to a military task, further research is needed to refine the use of tDCS in an attempt to achieve more practically significant performance changes.

The second study was designed to evaluate whether: 1) active tDCS would maintain or improve aviator performance over sham, 2) the timing of stimulation (*preflight* or *during flight*) to simulated flight significantly affected performance outcomes, and 3) the extent to which individual differences moderated those outcomes. Findings showed that application of tDCS *during flight* aids aviators in maintaining, or perhaps improving, performance at later points in the flight when individuals present with lower "behavioral activation system" activation. Moreover, this is particularly important for the effect of stimulation during the approach phase of flight. Given that participants were exposed to an unexpected emergency event prior to the approach, requiring them to re-plan the approach to some extent, the application of tDCS *during flight* aided in their maintenance of a more precise approach. This is key for considering how tDCS could be used prescriptively during long-duration missions where attention could wane and the necessity for maintaining performance is high. Finally, there are also some considerations to be made for the duration of stimulation delivery and its effect on other individual differences, namely inattentiveness, hyperactivity, and recency of experience. These individual differences were only significant in the moderation models for the *pre-turn* outcome data. Further research is needed to evaluate whether tDCS applied for longer durations and/or repeatedly can increase the duration of effects.

Given the variety of stimulation parameters used in the USAARL and reviewed studies, as well as differences in cognitive assessments used, it is not possible to recommend any form of transcranial stimulation for military use at this time. This issue was confirmed in a review of tDCS applied to the DLPFC in both healthy and neuropsychiatric samples, where an examination of stimulation parameters used across studies suggested that task accuracy was predicted by stimulation current, density, and density charge (Dedoncker et al., 2016). These would need to be

determined prior to recommending use of any form of transcranial electrical stimulation. However, in terms of plausibility, tDCS and its variants (e.g., alternating current) are the most suitable candidates for further examination due to established safety, low cost, and ease of application.

Technical Challenge 5: Deliver Interim Recommendations for Cognitive Enhancers For FVL Crews

In addition to the experimental studies conducted at the USAARL and the systematic review of the literature, we searched for other enhancement techniques currently being used by military services. The most ubiquitous approach for enhancing performance (or restoring performance) is the use of energy drinks and caffeine. However, research supporting enhancement properties (as opposed to performance sustainment or restoration) is limited. Additional approaches include specific cognitive training programs, many of which are employed during skill acquisition (learning or training), which are uniquely tailored to the occupation specialty, and lacking in program evaluation research to support. Enhancement is an active area of research and progress is expected in the coming years. However, at this time, additional techniques are not recommended for implementation.

Conclusion

At this time, there are a number of research questions that need to be answered before a final decision can be made in terms of implementing of any of the enhancement methodologies discussed here. However, results to date provide preliminary support for both pharmaceuticals and tDCS. Mixed efficacy results with respect to pharmaceuticals may be partially due to the role of individual differences and enhancement susceptibility, which is a research priority. Evaluation of these techniques to date has not incorporated the potential interactions between their effects and those associated with caffeine consumption and other “real-world” potentially confounding factors. Additionally, optimal parameters (e.g., stimulation locations, stimulation duration, stimulation timing, and pharmaceutical doses) are also key research priorities in the near-term.

In addition to the enhancement techniques under investigation currently, diligent monitoring of the field for other promising methods is needed. For example, testosterone therapy has shown mixed results in the civilian literature, particularly with older men, however, may not be applicable for use in the aviation environment. Monitoring of this research area (in progress at other U.S. Department of Defense research laboratories) is essential so that should results suggest the possibility for safe enhancement in a healthy, young population, this technique can be evaluated for efficacy in functional tasks (e.g., simulated flight).

Knowledge gaps are not the only potential challenges to consider in regards to recommendations. At this time, the research conducted and scheduled for execution does not meet the criteria of an Investigational New Drug or Investigational New Device by the Food and Drug Administration (FDA). However, it is unclear at this time if the research will remain exempt. For example, we may find that a factor (e.g., dosage) that increases risk associated with administration needs to be evaluated in which case FDA approval and oversight would be required.

Given our currently planned cognitive and functional performance enhancement research program, we anticipate providing an update on findings in the next two to three years. However, it is not possible at this time to estimate when, if ever, final recommendations and implementation strategies should be expected. In a best-case scenario, where findings are positive, side effects are minimal, and safe implementation methods are identified, we would anticipate recommendations to be prepared in the next five to ten years. Close monitoring of the research literature, regular communication with other researchers in the field, early planning for additional approvals (e.g., FDA), and execution of high-quality research studies are all essential, ongoing efforts to the timely transition of research to implementation.

References

Advokat, C. (2010). What are the cognitive effects of stimulant medications? Emphasis on adults with attention-deficit/hyperactivity disorder (ADHD). *Neuroscience & Biobehavioral Reviews, 34*(8), 1256-1266.

Battleday, R., & Brem, A. (2015). Modafinil for cognitive neuroenhancement in healthy non-sleep deprived subjects: A systematic review. *European Neuropsychopharmacology*, *25*(11), 1865-1881.

Broussard, G. J., Mytar, J., Li, R. C., & Klapstein, G. J. (2012). The role of inflammatory processes in Alzheimer's disease. *Inflammopharmacology*, *20*(3), 109-126.

Brunoni, A. R., & Vanderhasselt, M. A. (2014). Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: A systematic review and meta-analysis. *Brain and Cognition, 86*, 1-9.

Dedoncker, J., Brunoni, A. R., Baeken, C., & Vanderhasselt, M. A. (2016). A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: Influence of stimulation parameters. *Brain Stimulation 9,* 501-517.

Dunn, N. R., Pearce, G. L., & Shakir, S. A. W. (2000). Adverse effects associated with the use of donepezil in general practice in England. *Journal of Psychopharmacology*, *14*(4), 406-408.

Feltman, K.A., Kelley, A., Basso, J., King, M., & Chiaramonte, J. (2021). *Effects of non-invasive brain stimulation on soldiers' cognitive and functional performance* (USAARL-TECH-FR-2021-39). U.S. Army Aeromedical Research Laboratory.

Feltman, K. A., Mathews, C., Mackie, R., Morabito, C. P., & Kelley, A. M. (2021). *Transcranial electrical stimulation to sustain aviator performance: The effects of timing of stimulation and individual differences* (USAARL-TECH-FR-2021-42). U.S. Aeromedical Research Laboratory.

Fond, G., Micoulaud-Franchi, J. A., Macgregor, A., Richieri, R., Miot, S., Lopez, R., Abbar, M., Lancon, C., & Repantis, D. (2015). Neuroenhancement in healthy adults, part I: Pharmaceutical cognitive enhancement: A systematic review. *Journal of Clinical Research & Bioethics*, *6*(2), 1.

Hashemirad, F., Zoghi, M., Fitzgerald, P. B., & Jaberzadeh, S. (2016). The effect of anodal transcranial direct current stimulation on motor sequence learning in healthy individuals: A systematic review and meta-analysis. *Brain and cognition*, *102*, 1-12.

Kelley, A. M., Feltman, K., Nwala, E., Bernhardt, K., Hayes, A., Basso, J., & Matthews, C. (2019). *A systematic review of cognitive enhancement interventions for use in military operations* (USAARL-TECH-FR--2019-11). U.S. Army Aeromedical Research Laboratory.

Kelley, A. M., Goldie, C., Bernhardt, K., Curry, I. P., Crowley, J. S., Mathews, C., King, M. R., Chiaramonte, J. A., & Basso, J. (2021). *Enhancing operational performance in healthy rested Soldiers with pharmacological stimulants* (USAARL-TECH-FR--2021-016). U.S. Army Aeromedical Research Laboratory.

Linssen, A., Sambeth, A., Vuurman, E., & Riedel, W. (2014). Cognitive effects of methylphenidate in healthy volunteers: A review of single dose studies. *International Journal of Neuropsychopharmacology, 17*(6), 961-977.

Mancuso, L. E., Ilieva, I. P., Hamilton, R. H., & Farah, M. J. (2016). Does transcranial direct current stimulation improve healthy working memory? A meta-analytic review. *Journal of Cognitive Neuroscience, 28*(8), 1063-1089.

Reches, A., Laufer, I., Ziv, K., Cukierman, G., McEvoy, K., Ettinger, M., Knight, R. T., Gazzaley, A., & Geva, A. (2014). Network dynamics predict improvement in working memory performance following donepezil administration in healthy young adults. *NeuroImage, 88*, 228-241.

Repantis D, Schlattmann P, Laisney O, Heuser I. (2010). Modafinil and methylphenidate forneuroenhancement in healthy individuals: A systematic review. *Pharmacological Research, 62*, 187-206.

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