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A Systematic Review of Cognitive Enhancement Interventions for Use in Military Operations

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14. ABSTRACT

Future battlefield environments will require Soldiers to process large amounts of mission critical information within short periods and to interact with adaptive autonomous systems. Enhancing cognitive abilities such as sustaining attention over longer periods, more efficient processing of perceptual information, and quicker decision-making processes in these environments will promote mission success and operational effectiveness. The literature suggests numerous interventions for cognitive performance enhancement, including the use of stimulant agents, transcranial direct current stimulation, as well as others, some of which may be more appropriate for military settings. The purpose of this review was to summarize findings regarding the enhancement interventions from randomized, placebo-controlled, experimental research studies. While evidence supports the efficacy of some of the identified methods, further evaluations of not only the effectiveness and safety of these interventions but also the reliability and duration of effects are needed prior to implementation in military settings.

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Introduction

Cognitive enhancement is broadly defined as the amplification of human cognitive functioning in the bid to improve information-processing system (Bostrom & Sandberg, 2009). In much research, the term "cognitive enhancement" is used in a therapeutic sense with diseased populations to describe interventions for remedying specific pathology or functional impairment. For our purposes, however, we are interested in an alternate definition of the term, specifically research describing interventions that augment cognitive abilities beyond normal, healthy function. Cognitive subsystems targeted for enhancement include but are not limited to: (1) information retention – memory; (2) information selection – attention; (3) information acquisition – perception; (4) information representation – understanding; and (5) information outputs – reasoning and decision-making (Bostrom & Sandberg, 2009).

Soldiers operating in future environments will face complex situations in which they must attend to increasingly larger volumes of information in a very short time, requiring speedy processing of mission relevant information, and the necessity to 'decide faster' – one of the four Army Science & Technology Priorities. In order to do so, and to achieve cognitive dominance, Soldiers will need to sustain attention and process information rapidly. Research is needed to determine the effectiveness and operational safety of stimulant agents as well as other cognitive enhancement interventions on military-specific task performance and in operational settings. Operational settings include, but are not limited to, training environments, field operations, and deployment to combat zones.

Cognitive enhancement, especially through pharmaceutical intervention, is not a new concept to the military. The history of military use of performance enhancement drugs dates back to the medieval period with the advent of some particularly fearless Scandinavian class of warriors known as "berserkers" who used amanita muscaria mushroom stimulant drugs known as "fly agaric" to improve their physical and mental abilities (Anonymous, 2004). As the use of enhancement drugs in the military evolved over the centuries, the first and second world wars saw significant growth in the use of unregulated performance enhancement drugs, especially amphetamine, cocaine, and opium, with the German, British, French and American militaries as prominent users (Kamienski, 2016). Notably, Hitler's famous use of methamphetamine to enhance Nazi soldiers' performance remains a historical precedence. Nazi pilots were reportedly consuming large amounts of methamphetamine to help sustain their fighting strengths against adversaries (Ohler, 2017). Pharmaceutical enhancement amongst American troops continued during the Vietnam War where psychoactive substances like Dexedrine (dextroamphetamine), codeine, and Darvon (opioid) helped heighten a sense of invulnerability, bravado and alertness among Soldiers (Kamienski, 2016).

However, many of the historical methods for enhancement were discontinued as new information surfaced regarding the safety of the pharmaceuticals being used, to include their potential for addiction. Therefore, the history of performance enhancement interventions in military operations informs current policy regarding their use with respect to ethical considerations and safety. Balancing enhancement with the health of the Soldier is a key priority in determining how best to implement these interventions. Many of the interventions under consideration for use in military operations (pharmaceutical and non-pharmaceutical) have been primarily studied in diseased populations or have not been fully evaluated with respect to safety. This has resulted in limited knowledge for how effective they are at enhancing above baseline

function as well as their appropriateness for military populations and settings. Thus, the purpose of this systematic review was to synthesize the existing literature on potential cognitive enhancement strategies for use by the military. The criteria for this review were structured such as to include studies using strong research designs (e.g., placebo-controlled, random assignment). The objectives were then to: 1) identify interventions that may be appropriate for use in operational settings, and 2) to identify gaps in the literature and areas for future research.

Methods

Literature searches were conducted in mainstream databases, including Defense Technical Information Center (DTIC), PubMed/Medline, clinicaltrials.gov, and PsychInfo. The literature search included "gray" (difficult to locate) literature, which required the assistance of a professional librarian on staff at the U.S. Army Aeromedical Research Laboratory. The keywords included in the search are displayed in Table 1.

Table 1. Keywords Included in Literature Search

Categories	**Keywords**
Interventions	Modafinil
	Caffeine
	Pharmaceuticals
	Dopamine agonists
	Methylphenidate
	Exercise
	Nutrition
	Supplements
	Vitamins
	Training
	Sleep
	Mental strategies
	Transcranial stimulation
Cognitive Functions	Memory
	Attention
	Decision Making
	Judgments
	Cognition
	Enhancement
	Spatial abilities
	Visual perception
Enhancement	Performance
	Enhancement

Eligibility

The inclusion criteria were set to be conservative in order to increase homogeneity and ensure a high level of study quality. To be included in the systematic review, a study must have the following characteristics: a) random assignment, b) control group (between-subjects designs) or placebo-controlled (within-subjects designs), c) healthy human subjects aged 18-50 years, d) assessments of cognition-enhancement using valid and reliable cognitive performance measures,

e) published in the English language, and f) published between 2008 and 2018. Study exclusion and inclusion criteria are provided in Table 2.

Table 2. Study Inclusion and Exclusion Criteria

Criteria	Included	Excluded
Date published	2008-2018	Any prior to 2008
Study Designs	Within-subjects placebo-controlled	Non-random drug order
	Between-subjects with control group	Non-random assignment
Test Populations	Age: 18 to 50 years	Age: under 18 years and over 50 years
	Race: Any	Race: None
	Males and females	Gender: None
	Healthy	Unhealthy or abnormal
	Nationality: Any	Nationality: None
Interventions	Modafinil	None
	Caffeine	
	Pharmaceuticals	
	Dopamine agonists	
	Methylphenidate	
	Exercise	
	Nutrition	
	Supplements	
	Vitamins	
	Training	
	Mental strategies	
	Transcranial stimulation	
Language	English language	Non-English language
Outcome Measures	Valid and reliable	Not validated
	Neuropsychological tests of cognition	Not tested for reliability
	Measures of memory, attention, spatial reasoning, math reasoning, decision making, and judgment	Measures of mood, personality constructs, imaging studies

Exclusion criteria

The term cognition enhancement is used rather liberally in research. This review is focused on enhancement in specific areas of cognitive functioning. Therefore, studies that used only measures of mood, imagining, or other non-performance measures were excluded from the analysis given that the focus of the review is enhancement of *cognitive performance*. Also, studies using only measures of group performance (as opposed to individual performance) were excluded. All foreign language articles were excluded due to the lack of translation resources available to the investigators. Studies of unhealthy or abnormal populations, of humans under the age of 18 years or over the age of 50 years, or of animals were excluded. The use of healthy populations included populations who were not arbitrarily placed into abnormal circumstances, such as sleep deprivation protocols, in order to assess enhancement properties beyond their baseline function. Studies using measures of cognition that have not been validated or tested for reliability were excluded.

Procedure

The analysis was carried out according to the guidelines for systematic reviews and meta-analyses provided by Littell, Corcoran, and Pillai (2008) and Lipsy and Wilson (2001).

The research team first located potentially relevant studies using the search criteria specified above. The team then reviewed the titles and abstracts of the search results and requested full text versions of potentially relevant articles. All full text reports were reviewed for study eligibility. All eligible studies were independently read and reviewed by no less than two members of the research team. Minor discrepancies regarding eligibility were settled through discussion. The review process and results are provided in Table 3.

Table 3. Literature Search and Review Results

Search Results (January 2018)	3,807
Duplicated citations	550
Judged irrelevant or ineligible by title and abstract	2,937
Full text retrieved	320
Included studies	136

Results

Pharmaceuticals/Drugs

Sixty-two[*] articles were identified and reviewed, 37 of which did not meet the study criteria for inclusion. Nineteen articles were excluded because they were a review article (or meta-analysis), seven used animal models, seven were not experimental studies of cognitive enhancement, two were duplicates, one used an abnormal population, and two preceded the year 2008. Of the 25 included articles, majority of them studied modafinil (7 studies) or amphetamines (7 studies). Other drugs and drug classes studied includes selective serontin reuptake inhibitors (2 studies), methylphenidate (2 studies), cholinesterase inhibitors (2 studies), caffeine (2 studies), serotonin and norepinephrine reuptake inhibitors (2 studies), nootropics (1 study), selective inhibitor of cyclic guanosine monophosphate (1 study), nicotine (1 study), and antibiotics (1 study).[†] Table 4 provides a summary of enhancement effects.

[*] One article describes a combination of a drug and transcranial stimulation and thus appears in both sections of the results. This article is only counted once in Table 3.

[†] Note that the number of studies reported here exceeds the total number of articles included given that two articles studied more than one drug or drug class.

Table 4. Summary of Enhancement Effects with Pharmaceuticals/Drugs

Pharmaceuticals/Drugs

1. Main findings:
    a. Baseline level of performance moderated enhancement such that enhancement effects seen in low performers and not in high performers
    b. Variability in tasks used
    c. Many effects are dose or time dependent
    d. Consistent findings:
        i. Enhancement effects on attention tasks
        ii. No effects on working memory tasks
2. Design, individual differences, and sample sizes:
    a. Findings by gender were not reported
    b. Within subjects design – sample sizes range from 16-60 with significant effects
    c. Between subjects design – sample sizes range from 26-70 with significant effects

Drug	Dose	Construct Measured	Enhancement effect(s)
Modafinil	100mg	Abstract reasoning	Enhancement (compared to placebo) in low baseline performers (Esposito et al., 2013)
		Attention	Enhancement (compared to placebo) (Cope et al., 2017)
	200mg	Response inhibition	Enhancement (compared to placebo) (Mohamed et al., 2014)
		Implicit learning	Enhancement (compared to placebo) (Gilleen et al., 2014)
		Working memory	No enhancement (Gilleen et al., 2014)
		Attention	Enhancement (compared to placebo) (Ikeda et al., 2017; Cope et al., 2017)
		Learning	No enhancement (Cope et al., 2017)
		Alertness	No enhancement (Bellebaum et al., 2016)
		Impulsivity	No enhancement (Bellebaum et al., 2016)
	400mg	Alertness	Higher levels of alertness than placebo (Finke et al., 2010)
		Visual Perception Processing Speed	Enhancement (compared to placebo) seen in low baseline performers (Finke et al., 2010)
		Visual Short Term Memory	Enhancement (compared to placebo) seen in low baseline performers (Finke et al., 2010)
Methylphenidate	20mg	Associative Learning	Enhancement (compared to placebo) seen in high baseline performers (van der Schaaf, 2013) Performance deficits in low baseline performers (van der Schaaf, 2013)

	30mg	Error Awareness	Enhancement compared to placebo (reported effect size [Cohen's d' = 2.34]) (Hester, 2012)
	40mg	Alertness	Higher levels of alertness than placebo (Finke et al., 2013)
		Visual Perception Processing Speed	Enhancement (compared to placebo) seen in low baseline performers (Finke et al., 2013)
		Visual Short Term Memory	No enhancement (Finke et al., 2013)
Atomoxetine	60mg	Error Awareness	No enhancement (Hester, 2012)
Amoxetine and rTMS (combined)	60mg	Motor-sequence learning	Enhancement (compared to control) (Sczesny-Kaiser, 2014)
Citalopram	30mg	Error Awareness	No enhancement (Hester, 2012)
Amphetamine	10mg	Vigilance	No enhancement (MacQueen, 2018)
	20mg	Speed of Processing	Performance deficits in high baseline performers (Chou, 2013)
		Attention/Vigilance	Enhancement in low baseline performers (Chou, 2013)
		Working Memory	Performance deficits in high baseline performers (Chou, 2013)
		Verbal Learning	Performance deficits in high baseline performers (Chou, 2013) Enhancement in low baseline performers (Chou, 2013)
		Reason and Problem Solving	Enhancement in low baseline performers (Chou, 2013)
		Social Cognition	Performance deficits in high baseline performers (Chou, 2013)
		Visual Learning	Performance deficits in high baseline performers (Chou, 2013)
		Vigilance	Enhancement (compared to placebo) in 20mg dose group (MacQueen, 2018)
d-Amphetamine	10mg	Verbal Memory	Enhancement (compared to placebo) after a week daily, no immediate effects (Zeeuws 2010(a), Zeeuws, 2010(b)
Mixed amphetamine salts	10mg	Verbal Convergent Creative Thinking	No enhancement (Farah, 2009)
		Non-verbal Convergent Creative Thinking	Enhancement (compared to placebo) (Farah, 2009)
		Verbal Divergent Thinking	No enhancement (Farah, 2009)

		Non-verbal Divergent Thinking	No enhancement (Farah, 2009)
	20mg	Episodic Memory	Enhancement (compared to placebo) in low baseline performers (Ilieva, 2015)
		Working Memory	No enhancement (Ilieva, 2015)
		Inhibitory Control	No enhancement (Ilieva, 2015)
		Non-verbal Convergent Creativity	Enhancement (compared to placebo) in low baseline performers (Ilieva, 2015)
		Verbal convergent creativity	No enhancement (Ilieva, 2015)
		Non-verbal Intelligence	Enhancement (compared to placebo) in low baseline performers (Ilieva, 2015)
		Verbal and Mathematical Ability	No enhancement (Ilieva, 2015)
Ceretrophin (nutraceutical nootropic)	See note*	Abstract Reasoning	Enhancement (compared to pre-test and placebo group) (Stough, 2011)
Physostigmine	0.01 mg/kg per hour	Visual Attention	Enhancement (compared to placebo group) (Bauer, 2012)
Escitalopram	10mg	Executive Attention	Enhancement seen in acute (single dose and sub-chronic (daily for 7 days) dosage groups (compared to placebo) but effect moderated by familiarity with task (Drueke, 2009)
D-cycloserine	50mg	Visuospatial Construction and Nonverbal Memory	No enhancement (Otto et al., 2009)
		Logical Memory	No enhancement (Otto et al., 2009)
		Secondary Verbal Memory	No enhancement (Otto et al., 2009)
Donepezil	5mg	Visual Working Memory	No enhancement (Reches, 2014)
Caffeine	20mg	Attention	No enhancement
		Short term memory	Enhancement (as compared to placebo) when collapsing across three tasks (Davidson, et al., 2011)
		Long term memory	Enhancement (as compared to placebo) when collapsing across three tasks (Davidson, et al., 2011)
	200mg	Motor Memory	No enhancement (Hussain et al., 2015)

*huperzine A 150ug, Vinpocetine 15mg, Acetyl-l-carnitine 1500mg, r-alpha lipoic acid 400mg, rhodiola rosea 300mg, biotin 500ug

Herbal and Vitamin Supplements

The herbal and vital supplements studied included glucose, fish oil, fat, proteins, palm oil, and *Ginkgo biloba*. Thirty-one articles were retrieved and reviewed, 15 of which met eligibility criteria. Of those excluded, six did not include an experimental study of cognitive enhancement, six were reviews (or meta-analyses), two used animal models, and two used older adults. Table 5 presents a summary of the enhancement effects.

Table 5. Summary of Enhancement Effects with Herbal and Vitamin Supplements

Herbal and Vitamin Supplements

1. Main findings:
    a. Mixed effects for working memory tasks
    b. Many effects are does or time dependent
    c. Consistent effects seen with:
        i. Word recall tasks
        ii. Working memory tasks on general neuropsychological batteries
        iii. Information processing speed/accuracy/efficiency on general neuropsychological batteries
2. Design, individual differences, and sample sizes:
    a. Findings by gender are not reported
    b. Within subjects design – sample sizes range from 18-32 with significant effects
    c. Between subjects design – sample sizes range from 63-140 with significant effects

Supplement	**Dose**	**Construct(s) Measured**	**Enhancement effect(s)**
Brain-directed nutrients mixture	Multi-vitamin (≈1,448mg), fish oil (2.8g), brain enhancement supplement (≈1,424mg)	Executive Function	No enhancement (Amen et al., 2013)
		Reasoning	Enhancement (compared to placebo) (Amen et al., 2013)
		Memory	Enhancement (compared to placebo) (Amen et al., 2013)
		Information Processing Efficiency	Enhancement (compared to placebo) (Amen et al., 2013)
Palm leaf extract oil*	500mg	Working memory	Enhancement (compared to placebo) (Mohamed et al., 2013)
		Spatial learning	Enhancement (compared to placebo) following 2 months (Mohamed et al., 2013)
		Processing speed	Enhancement (compared to placebo) following 2 months (Mohamed et al., 2013)
DHA-rich fish oil	1g (daily dose for 12-week regiment)	Episodic Memory	No enhancement (Jackson et al., 2012)
		Attention	Enhancement (compared to placebo) (Jackson et al., 2012)

		Working Memory	No enhancement (Jackson et al., 2012)
EPA-rich fish oil	1g (daily dose for 12-week regiment)	Episodic Memory	No enhancement (Jackson et al., 2012)
		Attention	No enhancement (Jackson et al., 2012)
		Working Memory	No enhancement (Jackson et al., 2012)
Fat	16g vegetable oil	Attention	Enhancement (compared to placebo) (Jones et al., 2012)
		Working Memory	No enhancement (Jones et al., 2012)
Protein	40g	Attention	No enhancement (Jones et al., 2012)
		Working Memory	Enhancement (compared to placebo) (Jones et al., 2012)
Glucose	17g	Verbal Attention	Enhancement (compared to placebo) (An et al., 2015)
		Non-verbal Attention	Enhancement (compared to placebo) (An et al., 2015)
	25g	Episodic Memory	Enhancement (compared to placebo) (Brown et al., 2013)
		Attention	No enhancement (Brown et al., 2013)
		Associative learning	No enhancement (Stollery et al., 2014)
		Implicit Memory	No enhancement (Owen et al., 2010)
		Delayed Memory	No enhancement (Owen et al., 2010; Scholey et al., 2009)
		Immediate Memory	No enhancement (Owen et al., 2010)
		Spatial working memory	Enhancement (compared to placebo) (Owen et al., 2013)
		Working memory	Enhancement (compared to placebo) (Owen et al., 2013)
	40g	Attention	Enhancement (compared to placebo) (Jones et al., 2012)
		Working Memory	No enhancement (Jones et al., 2012)
	60g	Implicit Memory	Enhancement (compared to placebo) (Owen et al., 2010)
		Delayed Memory	Enhancement (compared to placebo) (Owen et al., 2010, 2013)
		Immediate Memory	No enhancement (Owen et al., 2010)

			Enhancement (compared to placebo) (Owen et al., 2013)
		Spatial working memory	Enhancement (compared to placebo) (Owen et al., 2013)
		Working memory	Enhancement (compared to placebo) (Owen et al., 2013)
	75g	Memory	No enhancement (MacPherson et al., 2015)
		Spatial ability	No enhancement (MacPherson et al., 2015)
Cytidine 5'-disphosphocoline	500mg	Verbal Learning	Enhancement (compared to placebo) in low baseline performers (Knott et al., 2015) Performance deficits in high baseline performers (Knott et al., 2015)
		Psychomotor Speed	Enhancement (compared to placebo) in low baseline performers (Knott et al., 2015)
		Working Memory	Enhancement (compared to placebo) in low baseline performers (Knott et al., 2015) Performance deficits in high baseline performers
		Executive Function	Enhancement (compared to placebo) in low baseline performers (Knott et al., 2015)
		Delayed Recall	Enhancement (compared to placebo) in low baseline performers (Knott et al., 2015) Performance deficits in high baseline performers (Knott et al., 2015)
		Attention	No enhancement (Knott et al., 2015)
	1000mg	Verbal Learning	Enhancement (compared to placebo) in low baseline performers (Knott et al., 2015) Performance deficits in high baseline performers (Knott et al., 2015)
		Psychomotor Speed	Enhancement (compared to placebo) in low baseline performers (Knott et al., 2015)
		Working Memory	Enhancement (compared to placebo) in low baseline performers (Knott et al., 2015)

			Performance deficits in high baseline performers
		Executive Function	Enhancement (compared to placebo) in low baseline performers (Knott et al., 2015)
		Delayed Recall	Enhancement (compared to placebo) in low baseline performers (Knott et al., 2015)
			Performance deficits in high baseline performers (Knott et al., 2015)
		Attention	No enhancement (Knott et al., 2015)
Bacopa monniera (Brahmi)	450mg	Working Memory	No enhancement (Sathyan-arayanan, et al., 2013)
		Information Processing Speed	No enhancement (Sathyan-arayanan, et al., 2013
		Attention	No enhancement (Sathyan-arayanan, et al., 2013
American ginseng	100mg	Working Memory	Enhancement (compared to placebo) (Scholey et al., 2010)
		Attention	Enhancement (compared to placebo) (Scholey et al., 2010)
		Information Processing Speed	No enhancement (Scholey et al., 2010)
	200mg	Working Memory	Enhancement (compared to placebo) (Scholey et al., 2010)
		Attention	Enhancement (compared to placebo) (Scholey et al., 2010)
		Information Processing Speed	No enhancement (Scholey et al., 2010)
	400mg	Working Memory	Enhancement (compared to placebo) (Scholey et al., 2010)
		Attention	Enhancement (compared to placebo) (Scholey et al., 2010)
		Information Processing Speed	No enhancement (Scholey et al., 2010)
Alpha Brain	≈2,545mg	Intelligence	No enhancement (Solomon et al., 2016)
		Logical Memory	No enhancement (Solomon et al., 2016)
		Visual Memory	No enhancement (Solomon et al., 2016)
		Verbal Memory	Enhancement (compared to placebo) after 45 days of

		consumption (Solomon et al., 2016)
	Attention	Higher levels of alertness than placebo (Solomon et al., 2016)
	Executive Function	Enhancement (compared to placebo) seen in low baseline performers (Solomon et al., 2016)
	Visual Short Term Memory	Enhancement (compared to placebo) seen in low baseline performers (Solomon et al., 2016)

*Study design details were not reported

Training

Forty-one* articles were reviewed and 16 met the eligibility criteria. Exclusions were due to lack of an experimental study (13 reviews, 1 statistical simulation), lack of cognitive performance measurements (7 studies), limited to a specialized or abnormal population (3 studies), and lack of enhancement strategy (1 study). Two types of training were evaluated primarily: neurofeedback training and task-specific training. Table 6 presents a summary of the enhancement effects.

Table 6. Summary of Enhancement Effects with Training

Training

1. Main findings:
    a. Neurofeedback training yielded mixed results
    b. Task training consistently produced enhancement effects
2. Design, individual differences, and sample sizes:
    a. Findings by gender are not reported
    b. Between subjects design – sample sizes range from 13-82 per group with significant effects
    c.

Training	Characteristics	Construct(s) Measured	Enhancement effect(s)
Neurofeedback training	Single session (25-30 minutes)	Executive function	No enhancement (Escolano et al., 2014)
		Attention	No enhancement (Escolano et al., 2014)
			Enhancement (compared to sham) (Escolano et al., 2014)

* One article describes a combination of training and exercise and thus appears in this section as well as the miscellaneous section of the results. This article is only counted once in Table 3.

		Working memory	Enhancement (compared to placebo) (Escolano et al., 2014)
		Verbal learning	No enhancement
	3 sessions/week for 4 weeks	Working memory	Enhancement (compared to baseline) (Hsueh et al., 2016)
	3 sessions, 10 minutes each	Motor learning	No enhancement (Rozengurt et al., 2016)
	1 session/week for 5 weeks	Attention	Enhancement (compared to control) (Sutarto, Wahab, & Zin, 2013)
	30 sessions (25 minutes/session, 5 sessions/week, 6 weeks)	Working memory	Enhancement (compared to control) (Sutarto, Wahab, & Zin, 2013)
	30 sessions (25 minutes/session, 5 sessions/week, 6 weeks)	Attention	No enhancement (Doppelmeyer, 2011)
		Spatial ability	Enhancement (compared to control) for sensorimotor rhythm neurofeedback training (Doppelmeyer, 2011)
Instrumental sensorimotor rhythm conditional training	10 sessions/ 1 hour per session	Declarative memory	Marginal enhancement (compared to control) (Hoedlmoser, 2008)
Haptic feedback	Force control task (maintain stable pressure on a wall with a stylus) during which stylus provided vibration cues	Focused attention	Enhancement (compared to controls) (Wang, 2014)
Task training	Exposure to familiar or novel images followed by a list of familiar words.	Working memory	Enhancement (compared to control) (Fenker, 2008; Moreau, 2015 [large effect sizes reported])
	Memory training using either verbal cues or imagery (90 minutes)	Working memory in spatial text processing	Enhancement in imagery group (compared to verbal cue group) (Gyselinck et al., 2009)
	Mental rotation training (45	Spatial cognition	Enhancement in mental rotation group (compared to control)

min/session for 6 sessions in 2 weeks)		(Meneghetti et al., 2011)
Semantic control training (45 min/session for 6 sessions)	Semantic processing	Enhancement (compared to control) (Metuki & Lavidor, 2013)
Mobile training application for distributed attention task (5 hours in 2 weeks)	Spatial attention	No enhancement (Rolle et al., 2017
Tracking task training (both experimental and control group completed task twice before test)	Attention	Enhancement (compared to control) (Strong & Alvarez, 2017)

Sleep

Forty-one articles were reviewed, nineteen articles of which met the eligibility criteria. Exclusions were due to lack of an experimental study (6 reviews, 2 commentaries, 4 correlational designs), lack of cognitive performance measurements (2 studies), lack of a control condition or group (7 studies), and abnormal conditions (sleep deprivation) (1 study). Majority of the included articles tested the utility of a nap (duration ranging from 20 to 90 minutes). Table 7 presents a summary of the enhancement effects.

Table 7. Summary of Enhancement Effects with Sleep/Napping

Sleep/Napping

1. Main findings:
    a. Inconsistent findings suggesting enhancement may be dependent on:
        i. REM, SWS, or non-REM durations
        ii. Individual differences in baseline ability
    b. Enhancements seen when the period between learning and testing was a night of sleep for motor sequence learning
2. Design, individual differences, and sample sizes:
    a. Findings by gender are not reported
    b. Between-subject designs were used in 16 of the included studies with sample sizes ranging from 9 to 40 per group
    c. Within-subject designs were used in 3 studies with sample sizes ranging from 15 to 32

Intervention	**Duration/ Characteristics**	**Construct(s) Measured**	**Enhancement effect(s)**
Single session nap	90-minute	Spatial learning/spatial memory	Enhancement (compared to control group) (Albouy, 2015;

			Diekelmann, 2012)
		Motor-sequence learning	No enhancement (Albouy, 2015; Backhaus, 2016)
		Probabilistic learning	Enhancement correlated with REM sleep amount; interference training following nap eliminated enhancement effects (Barsky, 2015)
		Working memory	Enhancement (compared to controls) (Lau et al., 2015)
	Delayed 90-minute nap (4 hours post learning)	Recognition memory	Enhancement (compared to controls and immediate nap groups) (Alger, 2010)
	Short (10-20 minutes)	Declarative memory	No enhancement (Backhaus, 2016)
		Visuomotor adaptation learning	No enhancement (Backhaus, 2016)
		Motor-sequence learning	No enhancement (Backhaus, 2016)
	40-minutes	Spatial learning/spatial memory	No enhancement (Diekelmann, 2012)
	Long (50-80 minutes)	Declarative memory	No enhancement (Backhaus, 2016)
		Visuomotor adaptation learning	No enhancement (Backhaus, 2016)
		Motor-sequence learning	No enhancement (Backhaus, 2016)
	2 hour (30 minutes of non-REM sleep)	Motor-sequence learning	No enhancement (Landry, 2016)
	REM sleep (60 or 90 minute nap)	Perceptual learning	Enhancement (compared to controls and non-REM sleep group) (Enhancement greatest for high performers; McDevitt, 2014)
	Non-REM sleep (60 or 90 minute nap)	Perceptual learning	No enhancement (compared to controls) (McDevitt, 2014)
		Declarative memory	Enhancement (compared to controls) (Enhancement greatest for high performers, Tucker, 2007)
Targeted memory reactivation during slow-	Presented during normal night of rest (~8hrs)	Explicit knowledge	Enhancement (compared to control) (Cousins, 2014)

wave sleep			
	90-minute nap	Emotional memory	Selective enhancement dependent on emotional salience (memory enhancement for highly emotional cues; Cairney, 2014)
Overnight sleep ("wake' group trained in morning and tested in evening, "sleep" group trained in evening and tested in morning	Testing delay of 12-hours	Motor-sequence learning	Enhancement (compared to control) (Debarnot, 2009; Brawn, 2010; Gregory, 2014; Malangre, 2016 [enhanced speed not accuracy]) No enhancement (Kemeny, 2016; Rickard, 2008)
		Emotional learning	Enhancement for "negative" images compared to "neutral (compared to control group) (Cunningham, 2014)
		Probabilistic learning	Enhancement (compared to control), effect moderated by performance level achieved during training (enhancement limited to low performers; Djonlagic, 2009) No enhancement (Kemeny, 2016)
		Sequence learning (grammar learning task)	No enhancement (Kemeny, 2016)
Sleep fragmentation	EEG micro-arousals (rate of 30+/hour)	Spatial attention	No enhancement (Ferri, 2010)
		Mental rotation	Enhancement (inconsistent across performance outcomes; Ferri, 2010)
		Selective attention	No enhancement (Ferri, 2010)
		Inhibition of return (attentional orienting)	No enhancement (Ferri, 2010)

Transcranial Stimulation

Ninety-two articles were reviewed, 47articles of which met the eligibility criteria. Exclusions were due to lack of an experimental study (1 review, 2 commentaries, 1 workshop overview), lack of cognitive performance measurements (26 studies), conditions not randomized (4 studies), lacked a control group (3 studies), older adult participants (2 studies), and published before 2008 (6 study). Majority of the included articles tested the utility of a transcranial direct current stimulation however, specific parameters varied between studies. Table 8 presents a summary of the enhancement effects.

Table 8. Summary of Enhancement Effects with Transcranial Stimulation

Transcranial Stimulation

1. Main findings:
    a. Mixed effects for tasks requiring executive functioning
    b. Mixed effects for creativity/object naming tasks
    c. Mixed effects on attention, though some consistency in quicker response times
    d. Mixed effects for decision making
    e. Mixed effects for working memory
    f. Consistent effects seen with:
        i. Learning tasks, however, type of learning differed (e.g., motor vs. language) – faster rate of learning found
        ii. Perception based tasks, with increased accuracy and reduced thresholds found
        iii. Visuospatial attention, increased accuracy
        iv. Recall tasks
2. Sample size:
    a. Findings by gender are not reported
    b. Within subjects design – sample sizes range from 9-120 with significant effects
    c. Between subjects design – sample sizes range from 24-48 with significant effects
3. Stimulation parameters are inconsistent across many studies

Intervention	**Type, intensity, location, duration**	**Construct(s) Measured**	**Enhancement effect(s)**
Transcranial Direct Current Stimulation (tDCS)	1 mA applied for 10 minutes to the frontal region	Working Memory	Enhancement (compared to sham-control; Andrews, 2011) Enhancement (compared to sham; Giglia, 2014)
	1 mA applied for 20 minutes to frontal region	Executive Function	Enhancement when applied to each hemisphere (compared to application to motor cortex and sham-control; Gbadeyan, 2016*)
		Learning	No enhancement for learning new material, enhancement of automaticity of already learned material (compared to sham-control and application to parietal area; Luculano, 2013) Enhancement (compared to sham-control; deVries, 2009)
		Perception / Attention	Enhancement (compared to 2 mA application and sham-control; Hoy, 2013) No enhancement (compared to 2 mA and sham-control; Teo, 2011) No enhancement (compared to sham-control; deVries, 2009)

1 mA applied twice for 10 minutes (total of 20 minutes of stimulation) to frontal region	Working memory	Enhancement with cathodal applied with a 10 minute interval between sessions and with continuous anodal application (compared to sham-control, each anodal and cathodal, and different timed intervals between stimulation applications; Carvahlo, 2014)
	Perception / Attention	Enhancement (compared to sham-control; Hsu, 2015)
1.5 mA applied for 15 minutes to frontal region	Executive Function	Enhancement (compared to sham-control, accuracy improved as a function of predictability; Sela, 2012)
	Working Memory	No enhancement (compared to sham-control; Steenbergen, 2016)
1.5 mA applied for 20 min to frontal region	Creativity / Cognitive Flexibility	Enhancement (compared to sham-control, increased creativity as a function of priming; Colombo, 2015)
	Perception / Attention	No Enhancement (compared to application to parietal region and sham-control; Roy, 2015)
2 mA applied for 8 & 10 minutes to frontal region	Creativity / Cognitive Flexibility	Enhancement when applied for 10 minutes (compared to sham-control; Fertonani, 2010)
2 mA applied for 20 minutes to frontal region	Learning	Enhancement (compared to temporal region and sham-control; Nikolin, 2015*)
	Memory	Enhancement (compared to sham-control; Matzen, 2015)
	Working Memory	No enhancement (compared to sham-control; Wang, 2016)
		No enhancement (compared to sham-control and tACS; Hoy, 2015)
		No enhancement (compared to 1 mA and sham-control; Hoy, 2013)
2 mA applied for 25 minutes to the frontal region	Attention / Decision Making	No enhancement (compared to sham-control; Smittenaar, 2014)
2 mA applied for 30 minutes to	Perception / Attention	Enhancement (compared to sham-control; Falcone, 2012)

frontal region		Enhancement (for alerting attention, compared to sham-control; Coffman, 2012)
	Working Memory	Enhancement (compared to sham-control; Trumbo, 2016) Enhancement when paired with training (compared to no-training sham-control and tDCS only; Martin, 2013)
1 mA applied for 20 minutes to parietal region	Learning	Enhancement (compared to frontal application and sham-control; Luculano, 2013) Enhancement (compared to sham-control; Meinzer, 2014)
1.5 mA applied for 20 minutes to parietal region	Perception / Attention	Enhancement when applied to right side (compared to sham-control, left side, and frontal region; Roy, 2015*)
1.5 mA applied for 15 minutes to parietal region	Perception / Attention	No enhancement (Weiss, 2012)
2 mA applied for 20 minutes to parietal region	Perception / Attention	Enhancement (compared to sham-control, occurred when placed on both hemispheres; Fujimoto, 2017)
2 mA applied for 30 minutes to parietal region	Perception / Attention	Enhancement when applied to right side (compared to sham-control and left side placement; Bolognini, 2010)
1 mA applied for 20 minutes to motor cortex	Learning	Enhancement with task-specific learning outcomes (Saucedo Marquez, 2013)
	Executive Function	No enhancement (when compared to frontal application and sham-control; Gbadeyan, 2016*)
2 mA applied for 20 minutes to the right cerebral hemisphere	Working Memory	No enhancement (Van Wessel, 2016)
2 mA applied for 13 minutes to temporal region	Memory	Enhancement with anodal placement on right hemisphere (compared to sham-control and left hemisphere placement; Chi, 2010)
2 mA applied for 20 minutes to	Learning	No enhancement (compared to sham-control and frontal region

	temporal region		placement; Nikolin, 2015*)
	2 mA applied for 20 minutes to cerebellum	Learning	Enhancement (compared to sham-control; Ferruci, 2013)
	1 mA applied for 20 minutes to primary somatosensory cortex	Perception / Attention	Enhanced when applied to both hemispheres (compared to single hemisphere application and sham-control; Fujimoto, 2014)
	1.5 mA applied for 20 minutes to occipital cortex	Memory	Enhanced when applied offline (compared to online and sham-control; Barbieri, 2016)
	0.7 mA applied for 570s intervals for 10 minutes to the frontal region	Attention / Decision Making	Enhancement when applied to left hemisphere (compared to right hemisphere application and sham-control; Filmer, 2017)
Oscillating tDCS	0 to 0.6 mA oscillating at 75 Hz for 25 minutes applied to frontal region during sleep	Memory	Enhancement for motor recall but not paired word associations (compared to sham-stimulation; Sahlem, 2015)
Intermittent theta-burst stimulation (iTBS)	3 pulses of stimulation at 50 Hz delivered during a 2s train repeated every 10s for total of 190s, this was repeated every 200ms for a total of 600 pulses; applied to frontal region	Working Memory	Enhancement (compared to sham-control; Hoy, 2016)
		Sustained attention	Enhancement only when applied to cortical dorsal attention network (compared to sham-control) greatest degree seen in low-baseline performers (Esterman, 2017)
		Transient attentional control	Enhancement (compared to sham-control) (Esterman, 2017)
Transcranial Alternating Current Stimulation (tACS)	1500 μA at frequencies of 40, 60 or 80 Hz for 45 minutes or 15 minutes to the	Perception / Attention	Enhancement with 60 Hz application (compared to 40 Hz, 80 Hz, and sham-control; Laczo, 2012)

	visual cortex		
	Between -750 μA and 750 μA at frequency of 40 Hz delivered for 20 minutes to frontal region	Working Memory	Enhancement as a function of load (compared to tDCS and sham-control; Hoy, 2015)
	Theta-tACS, 6Hz, temporo-parietal cortex, 20 min	Associative learning	Enhancement (compared to sham group) (Antonenko, 2016)
	Gamma-tACS, 40Hz, dorso-lateral pre-frontal cortex, 20 min	Working memory	Enhancement (compared to sham and tDCS groups) limited to higher workload version of task (Hoy, 2015)
	6 Hz, left and right frontal cortex, 11 min	Reversal learning	Enhancement (compared to sham group) in faster learning but deficit in rule-application behavior (Wischnewski, 2016)
Repetitive transcranial magnetic stimulation (rTMS)	1 Hz, primary motor cortex, 10 min	Visuomotor skill	No enhancement (Borich, 2011)
	1 Hz, right and left dorsolateral prefrontal cortex, 6 min	Contextual reasoning	Enhancement (compared to sham) (Tulviste, 2016)
		Visuospatial working memory	No enhancement (Tulviste, 2016)
	10 Hz, lateral occipital cortex, 1050 pulses	Visual selective attention	Enhancement (compared to sham) when applied in early stages of task execution (Estocinova, 2016)
	10 Hz, right and left dorsolateral prefrontal cortex, 6 min	Contextual reasoning	Enhancement left-side only (compared to sham) (Tulviste, 2016)
		Visuospatial working memory	No enhancement (Tulviste, 2016)
	5 HZ, lateral occipital complex or premotor cortex, 7s prior to task onset or during task	Working memory	Enhancement (compared to sham) when applied to lateral occipital complex, deficit when applied to premotor cortex *during* task; Enhancement (compared to sham) when applied to premotor cortex *prior to* task (Luber, 2017)

	20 Hz, targeted hippocampal cortical networks, 20 min/day, 5 consecutive days	Relational memory	Enhancement (compared to sham) that persisted an average of 15 days post-treatment (Wang, 2015)
rTMS and Amoxetine (60mg)	10 Hz, primary motor cortex, 10 minutes	Motor-sequence learning	Enhancement (compared to sham) (Sczesny-Kaiser, 2014) No enhancement (Backhaus, 2016)

Note. * studies compared stimulation at different brain regions and reported twice within the table.

Miscellaneous

Fifty articles were assessed and reviewed spanning 15 cognitive enhancement interventions including energy drinks, meditation, light therapy, psychosocial stress, oxygen, music, exercise, sensory deprivation, aroma therapy, haptic feedback, dreaming, suspense/anticipation, cuing, mental strategies, video games, and enhanced water. Fifteen of the articles met eligibility criteria. Reasons for exclusion included no cognitive measures (16 studies), review or commentary (6 articles), lack of control condition/group (5 studies), quasi-experimental or correlational design (4 studies), published before 2008 (2 studies), use of animal models (1 study), and use of a novel task (1 study). Summary of findings is presented in Table 9.

Table 9. Summary of Enhancement Effects with Miscellaneous Cognitive Enhancement Interventions

Miscellaneous Interventions

1. Main findings:
    a. Positive enhancement effects seen with exercise interventions for executive function and spatial ability
    b. Inconsistent findings for studies of meditation
2. Design, individual differences, and sample sizes:
    a. Findings by gender are not reported
    b. Between-subject designs were used in 7 of the included studies with sample sizes ranging from 6 to 31 per group
    c. Within-subject designs were used in 7 studies with sample sizes ranging from 15 to 52

Intervention	**Duration/ Characteristics**	**Construct(s) Measured**	**Enhancement effect(s)**
Video games	Ten 1-hour sessions playing action game (driving or first-person-shooter)	Visuomotor control	Enhancement (compared to control group) ($\eta^2 = 0.41$, Li, 2016)
Energy drinks	Red Bull* (250ml)	Sustained attention accuracy and speed	No enhancement (Wesnes, 2017)

		Working memory accuracy and speed	Enhancement (compared to controls and Sugar-free Red Bull, medium effect size) (Wesnes, 2017)
	Sugar-free Red Bull** (250ml)	Sustained attention accuracy and speed	No enhancement (Wesnes, 2017)
		Working memory accuracy and speed	No enhancement (Wesnes, 2017)
Enhanced water	A menthane carboxamide based cooling agent and citric acid added to water served at -17 degrees C	Sustained attention	Enhancement (compared to controls) (Labbe, 2010)
Exercise	Aerobic (20-minutes)	Attention	No enhancement (Lowe, 2016; Popovich, 2015)
	Aerobic (40-minutes	Spatial ability	Enhancement (compared to controls, limited to subset of tasks) (Moreau, 2015 [large effect sizes reported])
		Working memory	No enhancement (Moreau, 2015)
		Executive function	Enhancement *during* low-intensity exercise (Wohlwend, 2017)
			Enhancement *after* high-intensity exercise (Wohlwend, 2017)
	Designed sport (freestyle wrestling, 40-minutes	Spatial ability	Enhancement (compared to controls) (Moreau, 2015 [large effect sizes reported])
		Working memory	Enhancement (compared to controls) (Moreau, 2015 [large effect sizes reported])
Meditation	Mindfulness-Based Stress Reduction (2.5-hour	Sustained and selective attention	No enhancement (MacCoon, 2014)

	session/week for 8 weeks)		
	Meditation training program (2 weeks, 20-minutes mediation daily)	Metacognitive ability - memory	Enhancement (compared to controls) (Baird, 2014)
		Metacognitive ability - perception	No enhancement (Baird, 2014)
		Working memory	Enhancement (compared to controls) (Mrazek, 2013)
	Progressive Muscle Relaxation (11-minute session)	Derived relations	Enhancement (compared to control, $\eta 2$ = .33) (Tyndall, 2016)
Music	Background music in synchrony with presentation of visual stimuli	Visual processing	Enhancement (compared to control, $\eta 2$ = 0.198) (Escoffier, 2010)
	Background music during learning	Verbal learning	No enhancement (Jancke, 2010)
Psychosocial stress	Trier Social Stress Task (includes preparing and delivering a speech, math)	Priming non-declarative memory	Enhancement (compared to controls) (Hidalgo, 2012)
		Priming declarative memory	No enhancement (Hidalgo, 2012)
Oxygen	100% pure oxygen in a chamber under 2.0 absolute atmospheric pressure (80-minutes/day for 5 days)	Spatial working memory	Enhancement (compared to controls) (Yu, 2015)
		Immediate memory	No enhancement (Yu, 2015)
		Digital working memory	No enhancement (Yu, 2015)
		Attention	No enhancement (Yu, 2015)
		Long term memory	No enhancement (Yu, 2015)

* Red Bull (250ml) contains caffeine (80 mg), taurine (1000 mg), B-group vitamins (B3, B5, B6, B12), glucose (27 g), alpine spring water
**Sugar-free Red Bull (250ml) contains caffeine (80 mg), taurine (1000 mg), B-group vitamins (B3, B5, B6, B12), aspartame and acesulfame k, and alpine spring water

Discussion

The goal of this systematic literature review was to identify and summarize evidence for and against cognitive enhancement interventions for potential use with Soldiers in operational settings. We reviewed literature on both pharmaceutical and non-pharmaceutical interventions in an effort to summarize the current state-of-the science (years 2008-2018) regarding utility and efficacy of these methods for enhancement purposes. Overall, working memory enhancement and selective attention (using the Stroop Test) were the most consistently studied cognitive functions among the included studies. Inconsistent findings across all studies may be a reflection of true differences in effects or may be driven by methodology such as different tasks used to measure the same constructs or individual differences. A key finding reported in many studies is the moderating effect of baseline performance on enhancement (enhancement was seen in low performers and deficits in high performers) which has important implications for use in military settings. Specifically, some interventions may not be appropriate or effective in highly skilled or highly trained operators such as aviators. Below, we discuss the results of each intervention category in the context of feasibility for use in military settings.

Pharmaceutical Interventions

A total of eleven drugs and drug classes were identified in this review for enhancement purposes. The most researched drug in this review was modafinil with studies of doses ranging from 100-400 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, Schlattmann, Laisney, & Heuser, 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). Overall, modafinil may be useful for enhancement in 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, and 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 simple tasks and sustained attention yet inappropriate for more complex tasks and selective attention given increases in impulsivity following administration (Advokat, 2010). With regard to side effects, 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 present 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.

The enhancement results for the other drugs and drug classes included in this review (selective serontin reuptake inhibitors cholinesterase inhibitors, caffeine, serotonin and norepinephrine reuptake inhibitors, nootropics, selective inhibitor of cyclic guanosine monophosphate, nicotine, and antibiotics) were mixed. Specifically, the enhancement evidence for caffeine was mixed with positive findings limited to short- and long-term memory recall tasks. 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.

Herbal and Vitamin Supplements

Eleven herbal and vitamin supplements were identified in this review for enhancement purposes. The most researched of which was glucose with studies of doses ranging from 17-75 mg. Working memory was most consistently enhanced across the studies despite differences in methodology. This is consistent with published literature reviews suggesting memory enhancement in healthy adults in normal conditions (Smith, Riby, van Eekelen, & Foster, 2011). Note that this review found episodic memory to be most consistently enhanced. There did not appear to be a clear pattern with respect to dosage (e.g., effects were not seen with one dose level and not others) and inconsistent results likely are reflections of differences in methodology or individual differences. Interestingly, the enhancement effects of palm leaf extract oil were studied in the long-term (following two months of use) whereas majority of the other studies were more short-term or single-dose in nature. Enhancement was found for palm leaf extract oil but only one study was identified (Mohamed et al., 2013). Nearly all studies including fish oil yielded null effects. Our review did not find support for Bacopa, which is inconsistent with past

reviews. Specifically, Neale, Camfield, Reay, Stough, & Scholey, 2012 conducted a meta-analysis comparing effect sizes for enhancement by nutraceuticals (bacopa and ginseng) and modafinil and found that the nutraceuticals were nearly as effective as modafinil at enhancing cognition. Our review did find support, however, for ginseng enhancing working memory and attention but not information processing. Use of nutraceuticals and vitamins is very attractive given the lack of habit-forming properties but the literature is mixed and further replication studies are needed.

Training

A total of four forms of training were included within the review. These included neurofeedback training (5 studies), instrumental sensorimotor rhythm conditional training (1 study), haptic feedback (1 study), and task training (6 studies). Results from neurofeedback training studies suggest that repeated sessions over time may be more beneficial than single sessions given that single sessions produced mixed results and multiple sessions more consistently produced enhancement effects. Additionally, enhancement of working memory and attention were most commonly seen within the literature, suggesting these constructs may be more likely to benefit from neurofeedback training. The task training studies consistently showed positive effects in attention, working memory, and spatial cognition tasks. However, due to the variability of tasks trained on and methods used, it is difficult to evaluate whether task training would provide benefit to the military. Needed are studies examining the transferability of training on tasks specific to a cognitive construct onto operational tasks.

Sleep

Methods of targeted sleep interventions for cognitive enhancement that were reviewed included single session naps (9 studies), memory reactivation during slow-wave sleep (2 studies), overnight sleep (8 studies), and fragmented sleep (1 study). Enhancement following naps appears to be moderated by the duration of REM sleep acquired as well as the type of cognitive ability tested. Specifically, results seem to be strongest for perceptual learning and declarative memory. Training prior to a wake-day or sleep-night also appears to affect subsequent performance such that those who are tested following sleep show greater gains in performance than those tested before a night of sleep. These enhancements were seen for emotional, probabilistic, and motor-sequence learning.

Transcranial Stimulation

Five forms of transcranial stimulation were identified for enhancement purposes within this review. These included transcranial direct current stimulation (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 (6 studies including1 combined with amoxetine). Amongst 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 the 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 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 DLPFC *during* working memory training appeared to have the greatest potential (Mancuso, Ilieva, Hamilton, & Farah, 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).

Given the variety of stimulation parameters used in the 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 were predicted by stimulation current, density, and density charge (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016). These would need to be remedied prior to recommending use of any form of transcranial 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 costs, and ease of application.

Miscellaneous

Of the additional interventions identified in the review, exercise appears to have some potential for use such that aerobic exercise enhanced executive function and spatial ability but not working memory. Energy drinks did not produce enhancement effects whereas meditation did tend to show enhancement in higher-order processes.

Limitations

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 (stimulants and transcranial direct stimulations). Also, some interventions with potential for enhancement were not picked up using this approach. For example, macular pigment is a promising intervention approach shown to enhance visual performance but was not identified in our literature searches. Similarly, not all articles on a particular intervention were captured which is particularly a problem for underrepresented approaches since the conclusions are unfairly based on one or two studies. Considering these limitations is important when drawing conclusions about the utility of a particular intervention, and more so important when interpreting our findings with respect to an underrepresented topic.

Recommendations for Future Research

Additional research is needed prior to implementation of cognitive enhancement interventions in military settings. Missing from the literature overall are studies examining the

post-enhancement effects of these interventions. Specifically, whether dosing a Soldier with a stimulant or transcranial stimulation has lasting effects beyond the enhancement period that could negatively affect subsequent function such as negative impacts on sleep. Impaired sleep quality or duration could potentially compromise the next day's performance which, depending on mission needs, could be a substantially limiting factor. Also, secondary effects during the enhancement period were not consistently reported in studies. Some of the interventions summarized may have considerable negative side effects (e.g., increased risk-taking, increased impulsivity) that would override any benefit from enhancement. Systematic evaluation of side effects associated with enhancement interventions that include assessment of those that would be particularly detrimental in an operational setting, such as increased impulsivity, are required. Ideally such studies would be done in conjunction with evaluation of performance on military tasks using a military population, as similar examination within the general population may result different risk-taking decisions based on past experiences.

Conclusions

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 stimulation, which may be a reflection of the amount of attention given to these interventions and not purely strength of the interventions' effects. Much is unknown with respect secondary effects and post-enhancement effects for these interventions and further research is needed to understand the most advantageous implementation strategies.

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