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Enhancing Operational Performance In Healthy Rested Soldiers with Pharmacological Stimulants

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14. ABSTRACT

Considerable research has documented the optimization utility of stimulants in sleep deprived Soldiers and aviators, however, the research for enhancement purposes has demonstrated mixed results. One significant factor that may influence enhancement properties is general intelligence such that low performers exhibit stronger enhancement effects than high performers. The objectives of this study were to: 1) determine whether stimulants (specifically, modafinil and mixed amphetamine salts) can enhance Soldier cognitive abilities and performance on military tasks while controlling for baseline intelligence, and 2) to document adverse or undesirable side effects of each stimulant. To do so, a within-subjects design was employed using healthy, rested Soldiers and measuring performance on a set of basic cognitive assessments and operationally relevant tasks. Results show that mixed amphetamine salts may be effective at enhancing functional performance in healthy, rested Soldiers, specifically marksmanship. The study results, overall, do not provide support for 200 mg of modafinil enhancing performance in healthy, rested Soldiers.

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performance enhancement, stimulants, modafinil, cognitive enhancement, cognitive performance

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14. Abstract (continued)
The undesirable side effects seen with mixed amphetamine salts included a change in risk-taking attitudes, specifically, a propensity towards thrill-seeking, and physical symptoms (dry mouth, headache, jitteriness, feelings of aggression). However, these physical symptoms were very rare (less than 8% reported any single symptom).

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Introduction

Considerable research has documented the optimization utility of stimulants in sleep deprived Soldiers and aviators, however, the research for enhancement purposes has demonstrated mixed results. One significant factor that may influence enhancement properties is general intelligence such that low performers exhibit stronger enhancement effects than high performers. The objective of this study is to determine whether stimulants (specifically, modafinil, and mixed amphetamine salts [MAS]) can enhance Soldier cognitive abilities and performance on military tasks. To do so, a within-subjects design will be employed using healthy, rested Soldiers and measuring performance on a set of basic cognitive assessments and operationally relevant tasks.

Literature regarding the use of modafinil as a neuroenhancer in military operational settings continues to be lacking, with other forms of neuroenhancement, like transcranial direct current stimulation, being emphasized by the U.S. Air Force Research Laboratory (e.g., McIntire, McKinley, Goodyear, & Nelson, 2014; Nelson et al., 2015). The literature that has been published surrounding cognitive enhancement with the use of modafinil in military operations pertains to ameliorating performance decrements observed under sleep deprived conditions (e.g., Estrada et al., 2012); however, it is still unclear if modafinil can increase cognitive performance beyond normal baseline levels under operational conditions.

Several non-applied studies have explored the cognitive enhancing effects of modafinil on laboratory-based task performance in rested, healthy individuals. Recently, Cope et al. (2017) examined the effects of 200 and 400-milligram (mg) doses of modafinil on attention and executive functioning. Results indicated that compared to a placebo group, those that received either dose of modafinil improved target detection on a five choice continuous performance attention task. No effects were found for executive functioning. These performance results were also accompanied by no indication of hyperactivity as indicated by the Human Behavior Pattern test. The authors concluded that the effects of modafinil may be domain-specific and independent of an individual's level of arousal. In relation, Finke et al. (2010) reported that modafinil increased visual attention performance, specifically speed of processing and processing capacity, during a whole visual report task compared to placebo. However, these results were only evident in participants who were classified initially as lower performers. In a review of the literature on modafinil and cognitive enhancement, Battleday and Brem (2015) concluded that modafinil enhances aspects of executive function, in addition to enhancing attention to some degree. Note that some findings have been inconsistent in the literature (e.g., executive function).

Several authors have reported the effects of modafinil being tied to learning process. For example, Geng et al. (2013) investigated how modafinil influences probabilistic strategies for spatial attention and choice decisions. In their paradigm, subjects predicted whether a target would appear on the left or right side of a computer screen with a subsequent key response if the target appeared. The first half of the experiment was biased in that 70% of the targets occurred on one side of the screen and 30% occurred on the other. In the second half of the experiment, the target was presented randomly on both sides of the screen. Results indicated that modafinil increased probability rule learning rates. That is, compared to placebo, modafinil reduced the time for individuals to learn the probability distribution of the biased trials. Similarly, Pringle et

al. (2013) found increased implicit rule learning rates on an implicit compound learning task, but no effects on a digit span task. Finally, modafinil has been shown to increase implicit rule learning rates during a language learning task (Gilleen et al., 2014). Although implicit learning may be accelerated, there is no evidence to suggest that modafinil enhances transfer effects to new, untrained tasks (Gilleen et al., 2014). As a whole, these three studies indicate that modafinil may selectively increase implicit learning rates in rested, healthy individuals.

More applicable to operational settings, studies have also examined the effects of modafinil on complex cognition. Franke et al. (2017) compared the effects of methylphenidate, modafinil, and caffeine on chess playing performance and several common neuropsychological tasks. Subjects played 80 chess games against a computer adapted to player skill level over the course of four weeks under different drug intakes (caffeine, methylphenidate, modafinil, and placebo). Results indicated that modafinil, methylphenidate, and caffeine increased the amount of time chess players spent on deliberating chess moves, resulting in an increased number of games lost due to time constraints. However, after removing the games lost on time constraints, methylphenidate and modafinil increased performance compared to caffeine and placebo. No effects were found on standard neuropsychological tests (psychomotor vigilance test [PVT], trail making test, Stroop, Wisconsin card sorting, balloon analogue risk task, and Tower of Hanoi). Thus, the authors concluded that the effects of modafinil and methylphenidate result in a more reflective decision making process and may enhance performance under low temporal demands. Similar results were obtained by Mohamed and Lewis (2014) in which subjects on modafinil demonstrated increased response latencies on the Hayling Sentence Completion Test (a test of initiation speed and response suppression). Also pertinent to operational settings are varying task demands or workloads. Müller et al. (2013) reported that modafinil reduced error rates on a spatial working memory task and a visual pattern recognition task under more difficult task demands. Moreover, those on modafinil made fewer attempts to reach a correct solution during more difficult levels of a planning and decision making task (one touch stocking of Cambridge task).

In addition to overt task performance, subjective reports of alertness, mood, and motivation are also reported in several of the studies reviewed above. Of primary concern, reports of alertness, at least in terms of the studies reviewed here, are mixed. Some report modafinil increasing subjective alertness (Finke et al., 2010; Pringle et al., 2013) while Müller et al. (2013) reported no such effects. Modafinil also increased subjective reports of motivation, but did not influence reports of contentedness, tranquility, and calmness (Müller et al., 2013).

Overall, the recent literature on modafinil and cognitive enhancement suggests that compared to placebo, active medication enhances performance on basic attentional tasks and accelerates implicit learning rates. Moreover, modafinil increases deliberation times during complex tasks and reduced errors on spatial working memory tasks under higher task demands. The effects on subjective states generally show that subjects report increased alertness and motivation while on modafinil, with no effects on contentedness, tranquility, and calmness. The findings of the modafinil studies reviewed are summarized in Table 1.

Table 1. Summary of Modafinil Studies Examining its Efficacy in Cognitive Enhancement

Modafinil

Main findings and take away:

1. Measures:
    a. Mixed effects (e.g., Digit Symbol Substitution task)
    b. Mixed side effects and mood changes with all dosages
    c. Lower performers benefit more than higher performers
    d. Consistent effects seen with:
        i. Stroop
        ii. Digit span
        iii. Pattern recognition memory task
2. Sample size:
    a. Findings by gender are not reported
    b. Within-subjects design – sample sizes range from 11-18 with significant effects
    c. Between-subjects design – sample sizes range from 34-64 with significant effects

Construct	Measures/ Outcomes	Reference	Sample size	Dose	Design	Population
Attention	Complex-Theory of visual attention tasks	Finke et al., 2010	18 (9 males)	400 mg	Placebo, randomized, within-subjects, double-blind	Healthy non sleep deprived
Executive function	Wisconsin Sort Task	Cope et al., 2017	33 (26 males)	200/400 mg	Placebo, randomized, between subjects, double-blind	Healthy rested adults
Attention	5 choice continuous performance task	Cope et al., 2017	33 (26 males)	200/400 mg	Placebo, randomized, between subjects, double-blind	Healthy rested adults
Sustained attention	PVT	Franke et al., 2017	39 males	400 mg	Placebo, randomized, crossover (within-subjects relative to our purposes), double-blind	Healthy, rested chess players
Visual attention	Trail making test	Franke et al., 2017	39 males	400 mg	Placebo, randomized, crossover (within-subjects relative to our	Healthy, rested chess players

					purposes), double-blind	
Selective attention	Stroop	Franke et al., 2017	39 males	400 mg	Placebo, randomized, crossover (within-subjects relative to our purposes), double-blind	Healthy, rested chess players
Set shifting	Wisconsin Card sorting test	Franke et al., 2017	39 males	400 mg	Placebo, randomized, crossover (within-subjects relative to our purposes), double-blind	Healthy, rested chess players
Risk taking	Balloon Analogue Risk Task	Franke et al., 2017	39 males	400 mg	Placebo, randomized, crossover (within-subjects relative to our purposes), double-blind	Healthy, rested chess players
Problem solving	Tower of Hanoi	Franke et al., 2017	39 males	400 mg	Placebo, randomized, crossover (within-subjects relative to our purposes), double-blind	Healthy, rested chess players
Spatial probability	Task predicting location of target	Geng et al., 2013	26 (10 male)	200 mg	Placebo, randomized, crossover (within-subjects relative to our purposes), double-blind	Healthy, rested
Working memory	Letter memory task	Gillean et al., 2014	33 (13 male)	200 mg	Placebo, randomized, between-subjects, double-blind	Healthy, rested
Implicit learning	Language learning task	Gillean et al., 2014	33 (13 male)	200 mg	Placebo, randomized, between-	Healthy, rested

					subjects, double-blind	
Verbal learning	Modified California Verbal Learning test	Gillean et al., 2014	33 (13 male)	200 mg	Placebo, randomized, between-subjects, double-blind	Healthy, rested
General Neuropsych	MATRICS consensus cognitive battery	Gillean et al., 2014	33 (13 male)	200 mg	Placebo, randomized, between-subjects, double-blind	Healthy, rested
General Neuropsych	CogState	Gillean et al., 2014	33 (13 male)	200 mg	Placebo, randomized, between-subjects, double-blind	Healthy, rested
Attention	Detection of repeated numbers task	Baranski et al., 2004	18 males	400 mg	Placebo, randomized, within-subjects, double-blind	Healthy rested
Attention	Digit symbol substitution task	Makris et al., 2007	11 (5 males)	1.75/3.5/7 mg/ kilogram (kg)	Placebo, randomized, within-subjects, double-blind	Healthy, rested
Rule acquisition	Repeated Acquisition of Response Sequences Task	Makris et al., 2007	11 (5 males)	1.75/3.5/7 mg/kg	Placebo, randomized, within-subjects, double-blind	Healthy, rested
Short term verbal memory task	Sternberg number recognition task	Makris et al., 2007	11 (5 males)	1.75/3.5/7 mg/kg	Placebo, randomized, within-subjects, double-blind	Healthy, rested
Attention	Digit symbol substitution task	Marchant et al., 2009	24 (7 males)	200 mg	Placebo, randomized, between-subjects, double-blind	Healthy, rested
Short term visual memory	Delayed matching to sample task	Muller, 2004	16 (10 males)	200 mg	Placebo, randomized, within-subjects, double-blind	Healthy, rested
Executive function: planning,	Tower of Hanoi, spatial	Muller et al., 2013	64 (31 males)	200 mg	Placebo, randomized, between-	Healthy, rested

short term working memory, delayed memory	working memory task				subjects, double-blind	
Cognitive flexibility: rule acquisition Executive function: set shifting	Novel implicit learning task	Pringle et al., 2013	34 (17 males)	100 mg	Placebo, randomized, between-subjects, double-blind	Healthy, rested
Attention	Clock drawing	Randall et al., 2004	45 (20 males)	100/200 mg	Placebo, randomized, between-subjects, double-blind	Healthy, rested
Attention	Stroop	Randall et al., 2004	45 (20 males)	100/200 mg	Placebo, randomized, between-subjects, double-blind	Healthy, rested
Visual memory	Pattern recognition memory task	Randall et al., 2005	60 (29 males)	100/200 mg	Placebo, randomized, between-subjects, double-blind	Healthy, rested
Attention	Rapid visual information processing task	Randall et al., 2005	60 (29 males)	100/200 mg	Placebo, randomized, between-subjects, double-blind	Healthy, rested
Attention	Stroop	Randall et al., 2005	60 (29 males)	100/200 mg	Placebo, randomized, between-subjects, double-blind	Healthy, rested
Working memory	Digit span	Randall et al., 2005	60 (29 males)	100/200 mg	Placebo, randomized, between-subjects, double-blind	Healthy, rested
Attention	Mackworth clock task	Theunissen et al., 2009	16 (5 males)	200 mg	Placebo, randomized, within-subjects, double-blind	Healthy, rested

Planning	Tower of Hanoi	Turner et al., 2003	60 males	100/200 mg	Placebo, randomized, between-subjects, double-blind	Healthy, rested
Visual memory	Pattern recognition memory task	Turner et al., 2003	60 males	100/200 mg	Placebo, randomized, between-subjects, double-blind	Healthy, rested
Inhibitory control	Stop signal task	Turner et al., 2003	60 males	100/200 mg	Placebo, randomized, between-subjects, double-blind	Healthy, rested
Working memory	Digit span	Turner et al., 2003	60 males	100/200 mg	Placebo, randomized, between-subjects, double-blind	Healthy, rested

In addition to Modafinil, the cognitive enhancing effects of other stimulant medications, such as MAS, have also been explored. Ilieva et al. (2013) examined the effects of 20 mg of MAS on memory, working memory, inhibitory control, and creativity. Overall, results indicated no effect of MAS on cognitive performance. However, improvements were observed in initially lower performing individuals on an embedded figures task (a measure of convergent creativity) and word recall, with a trend toward improvements on Raven's Progressive Matrices (a non-verbal test of fluid intelligence). Similar results were obtained by Farah et al. (2009), in which improvements on an embedded figures task and Remote Associates Task (a measure of convergent thinking) were observed for initially low performing individuals. Moreover, Farah and colleagues also found detrimental effects of MAS on creativity performance for high performing individuals. In a review of the effects of stimulant medication performance on cognitive performance, Advokat (2010) concluded that amphetamine-based drugs, such as MAS, do not improve the acquisition of information, but help promote consolidation and increase information retention. Similar conclusions regarding consolidation and recall were reached in a review by Bagot and Kaminer (2013).

Recently, Cropsey et al. (2017) examined if subject expectations of performance enhancement while on MAS alter objective performance outcomes. In a within-subjects design, subjects were administered two, 10 mg doses of MAS or placebo over the course of four weeks and subjected to cognitive testing after each drug administration for a total of four trials (two on MAS and two on placebo). Subjects completed the California Verbal Learning Test-II, Wechsler Digit Span, Controlled Oral Word Associations Test, Connors Continuous Performance Task, and the Wechsler Test of Adult Reading. Subjects also reported whether they thought they received active medication or placebo and completed a subjective measure of task performance improvement. Overall, results indicated that subjects on MAS performed better on only two of

the 31 performance outcome measures of the test batteries compared to placebo. Specifically, these metrics were the California Verbal Learning Test's percentage of recall primacy and Connors Continuous Performance Task response style. Moreover, subjects were no better than chance at identifying whether they were receiving active medication or placebo; however, those receiving active medication rated themselves as performing better and objectively performed better on six of the 31 cognitive metrics. Thus, the authors concluded that MAS only has small enhancing effects on cognitive performance and these improvements may be driven by a placebo effect. However, the conclusion reached by Cropsey and colleagues (2017) runs in contrast to the findings of Ilieva et al. (2013), in which the authors reported no correlations between subject-perceived improvement in performance and actual performance. Thus, there still remains contradictory evidence as to potential placebo effects on cognitive enhancement with MAS.

The effects of dextroamphetamine (the primary active ingredient in MAS) on cognitive performance have also been studied with functional neuroimaging techniques. Samanez-Larkin et al. (2013) utilized positron emission tomography to uncover individual differences that modulate the effects of dextroamphetamine on task switching. Subjects received placebo or .43 mg/kg of dextroamphetamine on two separate occasions and performed a task requiring subjects to determine if a single digit presented in the top row of a 2 x 2 grid was greater than five and whether digits presented in the bottom row were odd or even. Performance results indicated that dextroamphetamine generally enhanced task switching performance. Furthermore, neuroimaging results indicated that subjects with more D2/D3 receptor availability in the lateral frontal and parietal cortices and the thalamus showed the most performance benefits from dextroamphetamine. The authors also reported a positive relationship between caudate nucleus dopamine release and task switching enhancement. The authors concluded that the effects of stimulant medication on cognitive performance are dependent upon individual differences in dopaminergic system composition.

In summary, the effects of MAS on cognitive performance generally fall in the domain of memory and attention, with small enhancing effects. Furthermore, there remains conflicting evidence as to the extent of placebo effects on objective performance outcomes. There is also evidence suggesting that MAS slightly enhances creativity in lower performing individuals, while reducing creativity in higher performing individuals. Moreover, individual differences in dopamine receptors and natural dopamine release may influence the effectiveness of the MAS additive dextroamphetamine. The findings of the MAS studies reviewed are summarized in Table 2.

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Table 2. Summary of MAS Studies Examining its Efficacy in Cognitive Enhancement

MAS

Main findings and take away:

1. Constructs and measures:
    a. Review article by Advokat (2010) suggests
        i. May be appropriate for enhancing simple tasks and sustained attention
        ii. May be inappropriate for more complex tasks and selective attention given increases in impulsivity
    b. Review article by Bagot and Kaminer (2013) suggests
        i. Effects consistently seen in enhanced cognitive processes in youth:
            1. Attention based tasks
            2. Reduced planning latency
            3. Consolidation of information leading to improved recall performance
    c. Inconsistent results and suspected publication bias may be "hiding" some null effects papers
    d. Lower performers benefit more than higher performers
    e. Review suggests the following tasks/assessments may be advantageous:
        i. Stroop
        ii. Digit span
        iii. Cognitive task switching
2. Sample size:
    a. Findings by gender are not reported
    b. Within-subjects design – sample sizes range from 16-46

Construct	Measures/Outcomes	Reference	Sample size	Dose	Design	Population	Effects observed
Episodic memory	International Affective Picture System	Ballard et al., 2014	31 (15 males)	10/20 mg	Placebo, counter-balanced, within-subjects, double-blind	Healthy	Increased errors
Intellectual ability	Weschler test of adult reading	Cropsey et al., 2017	32 (13 males)	10 mg	Placebo, counter-balanced, within-subjects, double-blind	Healthy rested college students	No effect
Verbal fluency	Controlled oral word association test	Cropsey et al., 2017	32 (13 males)	10 mg	Placebo, counter-balanced, within-subjects, double-blind	Healthy rested college students	No effect

Memory	Digit Span California verbal learning test	Cropsey et al., 2017	32 (13 males)	10 mg	Placebo, counter-balanced, within-subjects, double-blind	Healthy rested college students	Very small effect
Attention	Connor's continuous performance task Stroop Trail making test	Cropsey et al., 2017	32 (13 males)	10 mg	Placebo, counter-balanced, within-subjects, double-blind	Healthy rested college students	No effect
Creativity	Drawing task, remote association task	Farah et al., 2009	16 (4 males)	10 mg	Placebo, counter-balanced, within-subjects, double-blind	Healthy rested adults	Enhancement for low performers, Damaging effects for high performers
Memory Inhibitory control Creativity Fluid intelligence Scholastic intelligence	Face memory Word recall Word recognition Digit span Object 2 back Go/no-go Flanker Remote associations test Group embedded figures task Raven's advanced progressive matrices SAT	Ilieva et al., 2013	46 (22 male)	20 mg	Placebo, counter-balanced, within-subjects, double-blind	Healthy rested college students	No effect
Cognitive task switching	Classic paradigm as provided by Rogers & Monsel 1995	Samane z-Larkin et al., 2013	40 (21 males)	0.43 mg/kg	Placebo, within-subjects	Healthy rested college students	Effect only seen in low performers

Taken together, the civilian literature suggests that modafinil may be used to enhance basic cognitive processes whereas the results from MAS have been mixed. One possibility for the mixed results is a possible moderator variable, intelligence. The present study is designed to

establish whether this individual difference may limit application to a military population such that stimulants may prove unsuccessful with respect to performance enhancement for those with higher intelligence levels. This is particularly important when considering enhancement in specialized sub-populations such as aviators who have a higher level of general intelligence.

This study was designed to meet two objectives:

- Objective 1: To evaluate the utility of pharmaceuticals (MAS and modafinil) in enhancing human cognitive and military functional performance above baseline in healthy, rested volunteers whilst controlling for intelligence.

- Objective 2: To document any undesirable secondary effects including medically relevant side effects, increased risk-taking, and impulsivity.

Methods

This study employed a double-blind, randomized, placebo-controlled, within-subjects design. The independent variable was drug (modafinil 200 mg, MAS 10 mg, placebo) and abstract reasoning ability was included as a moderator variable. The primary outcomes were cognitive ability (attention, visual information processing, memory) and functional performance on two simulated military-relevant tasks.

Participants

Participants were 27 male, U.S. Army active-duty Soldiers. All participants were between the ages of 21 and 40 years (M = 32.93 years, SD = 4.44). Females were excluded given that the drugs administered could potentially negatively impact the very early stages of pregnancy. Normal (or corrected to normal) vision, hearing, and cognitive function were prerequisites for eligibility. Participants were required to sleep a minimum of 6 hours the night before participation, refrain from consumption of stimulants (including caffeine) and over-the-counter medications which may induce drowsiness for a minimum of 16 hours prior to each test session, alcohol and sedatives for 24 hours prior, and nicotine, 8 hours prior to all testing sessions, assessed by self-report. Participants were healthy such that they were free of the following exclusion criteria:

- Currently taking medications that induce drowsiness, such as over-the-counter antihistamines (assessed through self-report).

- Current medical conditions or medications affecting cognitive function or attention as determined by screening by study physician or medical practitioner.

- Current or recent use (as determined by study physician or medical practitioner) of medications that may interact with the test articles. Determined by self-report and exclusion at the discretion of the study physician or medical practitioner.

- Any history of any attention deficit condition requiring medication. A history of any attention deficit condition with medication is disqualifying as the potential interactions with testing are unknown and would therefore produce a potential

source of confounding or bias into the results of the study.

- Any history of psychological/psychiatric disorder.
- Any history of addiction or substance abuse as assessed through self-report.
- Any history of metabolic disorder such as dysthyriodism.
- Any history of significant cardiovascular disease or hypertension.
- Any history of hepatic or renal disorder.
- Any history of circulatory disorders given that mixed amphetamine salts can cause peripheral constriction of blood vessels.

Measures

Instruments and tasks used in this study are divided in three categories: questionnaires, cognitive tests, and military functional tasks.

Questionnaires.

All instruments were administered electronically with the exception of the Shipley Institute of Living scale, which was administered in hardcopy.

Adult Attention Deficit/Hyperactive Disorder (ADHD) Self Report Scale Symptom Checklist (ASRS).

The ASRS contains 18 items and requires 2 minutes for completion. It was developed in conjunction with the World Health Organization (WHO) and the Workgroup on Adult ADHD (Kessler et al., 2005) and is used as a screening tool with adult patients. The items are consistent with the Diagnostic and statistical manual of mental disorders, version IV criteria (American Psychiatric Association, 2000). For the purposes of this study, the scores were used to screen for symptoms associated with ADHD that could potentially confound the results.

Sleep Timing Questionnaire (STQ).

The STQ is an 18-item self-report measure of sleep habits shown to be valid (such that it correlates with sleep diary information) and reliable across repeated administrations (Monk, et al., 2003). This information was used in this study to identify any potential confounds pertaining to sleep disturbances or otherwise insufficient rest.

Karolinska Sleepiness Scale (KSS).

The KSS is a well-validated single item questionnaire that asks subjects to rate how sleepy they feel in the moment (Kaida et al., 2006). The KSS measures daytime sleepiness with higher scores indicating greater daytime sleepiness. This information was used to identify potential confounding factors. The KSS was administered twice on each test day: pre-dosing and

post-testing. Thus, for each test day, difference scores were calculated and analyzed in order to evaluate any changes in daytime sleepiness associated with each test article.

Beck's Depression Inventory (BDI).

Depression symptoms were measured using the Beck Depression Inventory- II (BDI-II; Beck, Steer, & Brown, 1996). The BDI-II is a commonly used 21-item, multiple-choice self-report which captures affect, cognition, and physical symptoms of depression over the most recent two week period. Higher scores indicate greater endorsement of depression symptoms. For the purposes of this study, the scores were used to screen for symptoms associated with depression and anxiety that could potentially confound the results.

Shipley Institute of Living Scale (SILS).

The SILS was designed to assess general intellectual functioning in adults and adolescents and to aid in detecting cognitive impairment in individuals with normal original intelligence. The SILS yields three major summary scores: Vocabulary, Abstract Reasoning, and combined Total scores. The Vocabulary sub-scale consists of 40 multiple-choice verbal reasoning questions, and primarily taps crystallized intelligence. The Abstract Reasoning subscale includes 20 series-completion items of inductive reasoning that tap fluid ability (Zachary, 1986). Convergent validity of both the Vocabulary and Abstraction measures with crystallized and fluid intelligence (respectively) has been assessed and confirmed in a general population (Matthews et al., 2011). For our purposes, the abstract reasoning subscore was used as a moderator variable in the analyses.

Profile of Mood States – Short Form (POMS-SF).

The POMS-SF is a valid and reliable short version of the POMS, a measure of psychological distress and mood (McNair et al., 1981). The POMS-SF contains 35 items, in each an adjective is provided and the subject rates how much it describes them using a 5-point Likert scale format (Curran et al., 1995). The POMS-SF was administered to evaluate the degree to which the test articles impacted mood states. The scale outputs 7 subscale scores: tension, anger, vigor, esteem-related affect, fatigue, depression, and confusion. Additionally, a total mood disturbance score is computed by summing the scores for the "negative" affect subscales (tension, anger, fatigue, depression, and confusion) and subtracting the "positive" affect subscales (vigor and esteem-related affect). The POMS-SF was administered twice on each test day: pre-dosing and post-testing. Thus, for each test day, difference scores were calculated and analyzed in order to evaluate any mood disturbances associated with each test article.

Evaluation of Risks Scale (EVAR).

The EVAR is a 24-item questionnaire that has been used effectively to measure individual variability in risk assessment in previous research with Special Operations Forces (Sicard, Jouve, & Blin, 2001). Individuals mark a point along a 100-millimeter (mm) bipolar visual analogue scale to indicate their preference for various types of risky activities. The scale yields five subscores: impulsiveness, self-control, energy, invisibility, and danger-seeking. This scale is included to evaluate the effect of the test articles on secondary outcomes.

Symptom Checklist.

A brief questionnaire developed in-house to assess the presence, severity, and onset of any side effects. Twelve possible symptoms are listed in the checklist as well as space to write in any additional symptoms.

Cognitive tests.

All tests were administered electronically.

Continuous Performance Test.

The Continuous performance test is a measure of impulsivity, specific to rapid response initiation (Conners & Sitarenios, 2011). In this task, participants are presented a series of letters and are instructed to respond when they see the identified "target" stimuli. Participants are presented with 360 trials with varied intervals of 1, 2, and 4 seconds. Accuracy, reaction time, and number of errors of commission errors are key dependent measures.

Stop Signal Task.

The stop signal test is a measure of impulsivity, specific to response inhibition (Logan et al., 1997). To complete the task, participants must respond as quickly as possible to signals identified as "go" signals and to inhibit responses identified as "stop" signals. Participants are presented with 512 trials every 2.5 seconds for approximately a 4-minute completion time. The primary dependent measures are the mean percent correct (accuracy), mean reaction time for correct trials (*correct-only*), and mean reaction time for all trials (*all-trials*). This task has been shown to be valid and reliable (e.g., Weafer et al., 2013).

Stroop Task.

The Stroop task is a well-established cognitive test of selective attention (Macleod, 1991). In this task, participants are presented with color words and must name the color that the word is printed in and ignore the meaning of the word. Participants complete 10 trials of each congruent and incongruent color-word pairs. Stroop effect interference is the key outcome measure and is the mean difference in reaction time between congruent and incongruent trials.

Digit Span Task.

The Digit Span task is a well-established cognitive test of working memory (Miller, 1956). Participants are presented strings of numbers in increasing length and must recall them. The task is complete when a participant cannot accurately recall the string of numbers of a particular length twice. The dependent measure is the longest string length accurately recalled.

Rapid Visual Information Processing Task (RVIP).

The RVIP is a well-validated measure of sustained attention (Bakan, 1959). In each trial, participants are presented with a sequence of digits ranging from 2 to 9 in length and must detect

"target" sequences within those presented. Difficulty is manipulated using the length of the "target" sequence as well as the speed of the sequence presentation (2 levels: slow [1,200 milliseconds (ms)], fast [600 ms]). Participants complete six blocks of trials.

Shifting Attention Task.

The Shifting Attention task (digit symbol substitution task) requires participants to "code" a set of digits with the provided symbols in 90 seconds (a total of 98 digits to code). The number of correctly coded digits is the dependent measure. This is a well-established measure of executive function, set shifting, and attention (Royer, 1971).

Military tasks.

Tasks were simulated using validated assessments.

Patrol-Exertion Multitask.

The Patrol-Exertion Multitask (PEMT) is a task developed and validated by Scherer and colleagues (2018) that requires participants to gather information from a 12-minute virtual reality scenario depicting a first-person patrol in Afghanistan while reporting observed improvised explosive device (IED) markers (figure 1). The scenario includes four "tactical pause" stops for IED marker identification with a total of 13 targets observed during the scenario. After completing the task, participants are asked 11 post-patrol questions related to their patrol experience (e.g., grid coordinates, clothing colors, time, date, enemy vehicles, presence of IED components, and weapons) to assess their attention and memory. While completing the task, participants continuously step on a 6-inch exercise step to simulate the demands of a patrol and maintain a heart rate between 65% and 85% of their age-predicted maximum heart rate, monitored using a wireless heart rate monitoring device. For safety purposes, if a participant was uncomfortable using the step, jogging in place was permitted as an alternative. Participants wore an Army combat helmet, clear eye protection, and carry a simulated M-4 weapon fitted with an instrumented trigger switch and audio cue transmitter. At 12 time points during the scenario, an audible tone cue was emitted from a speaker on the mock weapon. These tones were generated during periods of both minimal distractions and periods with multiple visual and auditory distractions. Participants were instructed to press the grip-mounted trigger switch as quickly as possible after each tone. The primary outcomes from this task, for our purposes, was the reaction time in response to the auditory stimuli, which is randomly presented within predetermined time intervals.

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Figure 1. Image reproduced from Scherer et al. (2018) and depicts administration of the patrol exertion task.

Standard Marksmanship Task.

In the standard marksmanship qualifying task, participants shoot at 40 targets presented sequentially using a rifle. The targets vary in distance, from 50 to 300 meters. The scenario entails the participant firing from three positions: prone supported, prone unsupported, and kneeling. The key dependent variables for these tasks are accuracy, reaction time, and throughput (accurate shots per second). The weapons simulator used for this task is the Engagement Skills Trainer (EST) 2000. The EST 2000 is a United States Army small arms training device. This system allows for weapons training in a controlled (simulated) environment. As can be seen in Figure 2, a participant fires from a lane (the U.S. Army Aeromedical Research Laboratory (USAARL) EST 2000 has a five lane configuration) at "targets" which appear on a projection screen at a distance of 26 feet 3 inches from the firing line. The weapons have been modified to use with the EST 2000 but maintain their form, fit, feel, and function. At the onset of this task, participants familiarized themselves with the weapons simulator and zeroed their weapon (i.e., aligned the laser sensor to the equivalent of the mechanical weapon zero).

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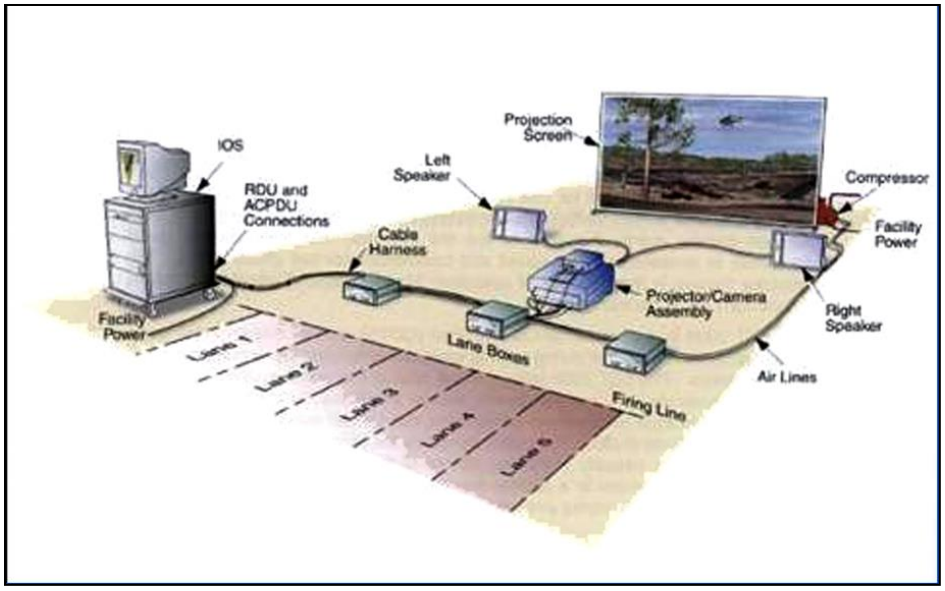

Figure 2. EST 2000 set-up (Anthony, 2006).

Procedure

Participants completed a total five sessions: consent/screening, baseline, test session 1, test session 2, and test session 3. Prior to each session (except consent/screening), participants were required to: abstain from medication inducing drowsiness, stimulants, and alcohol within the prior 16 hours; abstain from nicotine within the prior 8 hours; and sleep for a minimum of 6 hours. Sleep was estimated with the use of wrist-worn actigraphy device. In each session (except the consent/screening), the order of the cognitive tasks was randomized and target stimuli in the cognitive tasks were varied in order to minimize carryover and order effects. The four test sessions were separated by a minimum of two days to eliminate the possibility of drug carryover effects. Participants arrived at the laboratory at 0800 hours on each test day at which time they confirmed (or denied) adherence to the study criteria and a study team member checked the actigraphy device data. Participants then completed the symptom checklist, Karolinska Sleepiness Scale, and the POMS-SF to determine whether any physical symptoms were present prior to dosing (e.g., headaches) and any mood disturbances. At the three active test sessions (excluding baseline), participants were then administered a single, oral dose of modafinil (200 mg), MAS (10 mg), or placebo. Participants were monitored/supervised at all times following dosing until the study physician or medical practitioner released them for the day. Two hours following dosing, participants began testing. Activities and times associated for each session are outlined in table 3.

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Table 3. Time Required for Each Portion of Testing Session/participant Activities of Data Collection

Session	Participant Activity	Data collected	Approximate Time to Complete
1: Test scheduling, informed consent, and screening procedures	Informed Consent	Not Applicable (N/A)	30 minutes
	SILS	Abstraction Quotient Score, vocabulary score, total score	15 minutes
	Screening	N/A	10 minutes
	Actiwatch administration	N/A	2 minutes
Total time for Session 1			Approximately. 1 hour
2: Baseline test session	BDI	Total symptom score	2 minutes
	STQ	Sleep quantity, wake after sleep onset	3 minutes
	ADHD scale	Total scores (Part A and B)	2 minutes
	EVAR	Total and 3 subscale scores	5 minutes
	Marksmanship	Performance measures	40 minutes
	Cognitive tasks	Performance measures	35 minutes
	Patrol exertion task	Performance measures	20 minutes
Total time for Session 2			Approximately 1.5 hours
3-5: Drug administration test sessions	Dosing	N/A	10 minutes
	Recreational time	N/A	120 minutes
	POMS-SF	Total and 6 subscale scores	3 minutes
	Symptom Checklist	Symptom ratings	2 minutes
	Karolinska Sleepiness Scale	Sleepiness score	1 minute
	Marksmanship	Performance measures	40 minutes
	Patrol exertion task	Performance measures	20 minutes
	Cognitive tasks	Performance measures	35 minutes
	EVAR	Total and 3	5 minutes

		subscale scores	
	Recreational time	N/A	264 minutes (approximately 4.5 hours)
	Meet with Study Physician or Medical Practitioner to release for the day	N/A	10 minutes
Total time for Sessions 3-5 (per sessions)			Approximately 8 hours and 10 minutes

Blinding, randomization, and dosing.

Participants and the research team were both blind to the drug administered at each test session. All test medications and placebo were administered orally in capsules that had been rolled in sugar, to mask any potential taste, shape, size, or color differences. A web-based randomization system was used to create a random order of the test articles unique to each participant. After test articles were prepared (put in capsules), they were put into bags labeled by participant number and test session by an individual otherwise unaffiliated with the study. For safety purposes, a master drug list was maintained and stored in a password protected file in the event of a medical emergency (e.g., seizure) or adverse event (e.g., rash).

Statistical analysis and quality control

All data were inspected for impossible values and technical errors prior to analyses.

Objective 1.

The effects of modafinil and MAS were evaluated using repeated measures analyses of covariance (ANCOVAs) and multivariate ANCOVAs (MANCOVAs). Six models were run, one per cognitive test (Stroop, digit span, RVIP, shifting attention) and military task (marksmanship, patrol exertion). All outcome measures were independent of each other. Abstract reasoning was included as a covariate in order to control for baseline intelligence. A bonferroni correction was applied to minimize the risk of Type I error. Planned contrasts were used to evaluate differences between drug conditions.

Objective 2.

In order to document any undesirable secondary, four multivariate, repeated measures, analyses of covariance (MANCOVAs) were run: 1) POMS, 2) EVAR subscale scores, and 3) stop signal test, and 4) continuous performance test. All outcome measures were independent of each other. Abstract reasoning was included as a covariate in order to control for baseline intelligence. Planned contrasts were used to compare the modafinil and MAS conditions to the placebo condition. Frequencies of symptoms for each test article are reported.

Results

Two participants only completed the baseline assessments and are thus excluded from the analyses (n = 25). Additionally, outliers (standardized values exceeding 3) were also removed listwise from the individual analyses. Abstract reasoning score was included in analyses as a covariate (M = 34.16, SD = 4.47). Published normative data (Harnish et al., 1994) for the age groups represented in this study are mean abstract reasoning scores of 29.47 (SD = 7.46) for those 20-29 years and 29.64 (SD = 6.52) for those 30-39 years.

Objective 1

Stroop test.

Two outliers were removed from the analysis (n = 23). The results of the ANCOVA did not support an effect of drug condition on stroop effect, $F(2, 42) = 1.12$, $p = 0.34$.

Digit span test.

Two outliers were removed from the analysis (n = 23). The results of the ANCOVA did not support an effect of drug condition on digit span length, $F(2, 42)) = 2.71$, $p = 0.08$.

Rapid visual information processing test.

One participants' data did not record properly and is not included in the analyses (n = 24). Two one-way (drug: placebo, modafinil, MAS), repeated-measures MANCOVAs with abstract reasoning score as the covariate was run to evaluate effects on reaction time and d′ (sensitivity index). Two separate models were run, one for each presentation speed (fast, slow). No significant effects were found with d′. However, there was a significant interaction effect between drug condition and the covariate (abstract reasoning score) on reaction time, $F(2, 44) = 5.39$, $p = 0.008$. Figure 3 illustrates the relationship between the covariate and outcome variable for each drug condition. Planned contrasts show that reaction time was faster for modafinil (M = 421.19 ms, SE = 11.78) over that for placebo (M = 433.39 ms, SE = 14.54); whereas that for MAS (M = 428.41 ms, SE = 10.45) did not differ from that for placebo. Finally, in order to further understand how the relationship between abstract reasoning and performance changed by drug condition, Pearson's r correlation coefficients were calculated. For all conditions, the relationships were negative and ranged from very weak (nearly nonexistent) to slightly weak: placebo, $r(24) = -0.31$, $p = 0.14$; modafinil, $r(24) = -0.01$, $p = 0.95$; MAS, $r(24) = -0.37$, $p = 0.08$.

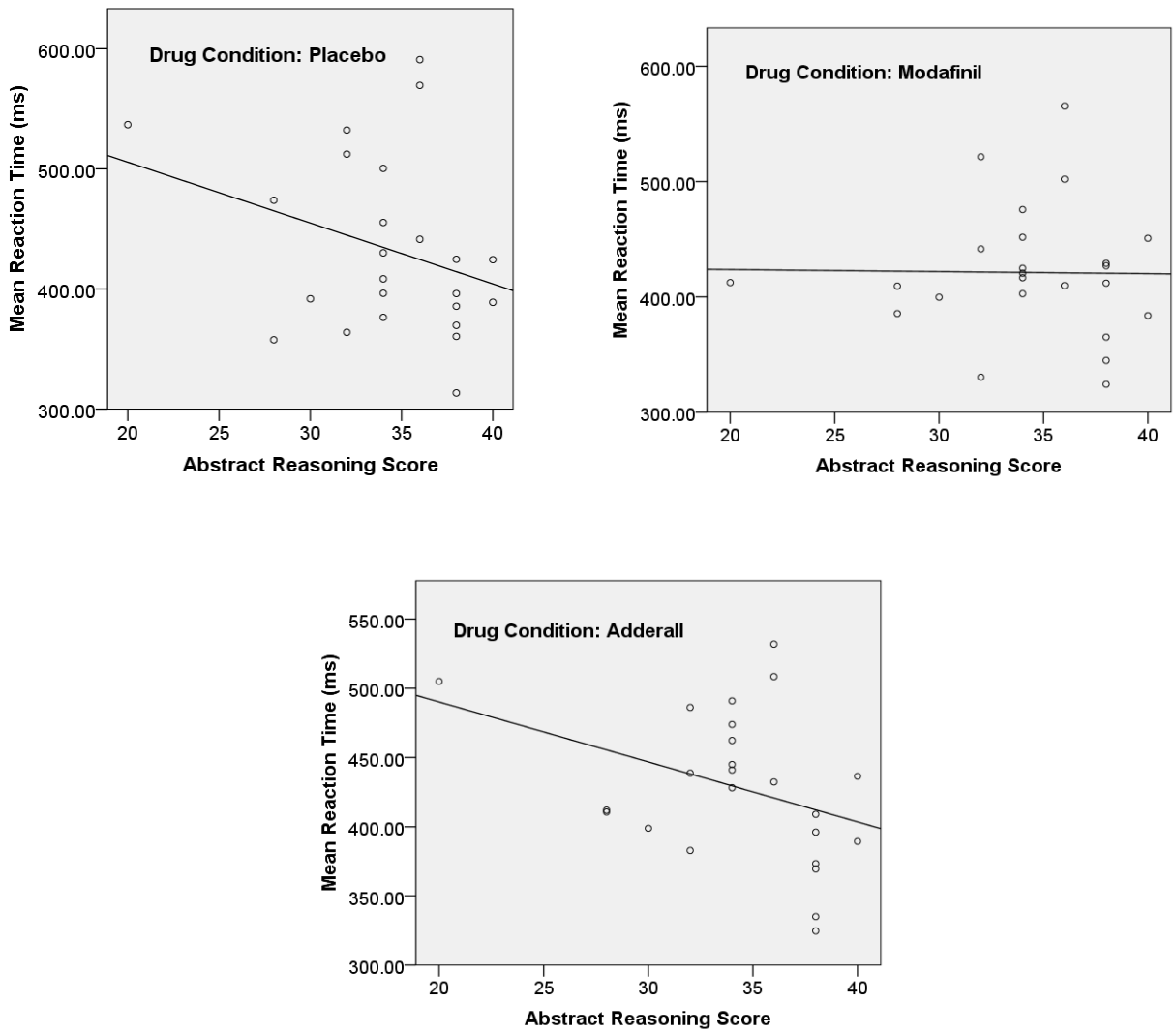

Figure 3. Relationship between mean reaction time on the RVIP (fast condition) and abstract reasoning score by drug.

The slow speed condition analysis yielded a congruent result; specifically, a significant interaction effect, $F(2, 44) = 3.97$, $p = 0.02$. Again, the modafinil condition showed faster reaction times ($M = 509.08$ ms, $SE = 21.93$) than placebo, ($M = 535.88$ ms, $SE = 24.05$), and no difference was seen between placebo and the MAS condition ($M = 511.58$ ms, $SE = 17.13$). Figure 4 illustrates the relationship between the covariate and outcome variable for each drug condition. Finally, in order to further understand how the relationship between abstract reasoning and performance changed by drug condition, Pearson's r correlation coefficients were calculated. For MAS and modafinil conditions, the relationships were negative, however weak, $r(24) = -0.16$, $p = 0.45$ and $r(24) = -0.26$, $p = 0.23$. The relationship was stronger and negative in the placebo condition, $r(24) = -0.50$, $p = 0.01$.

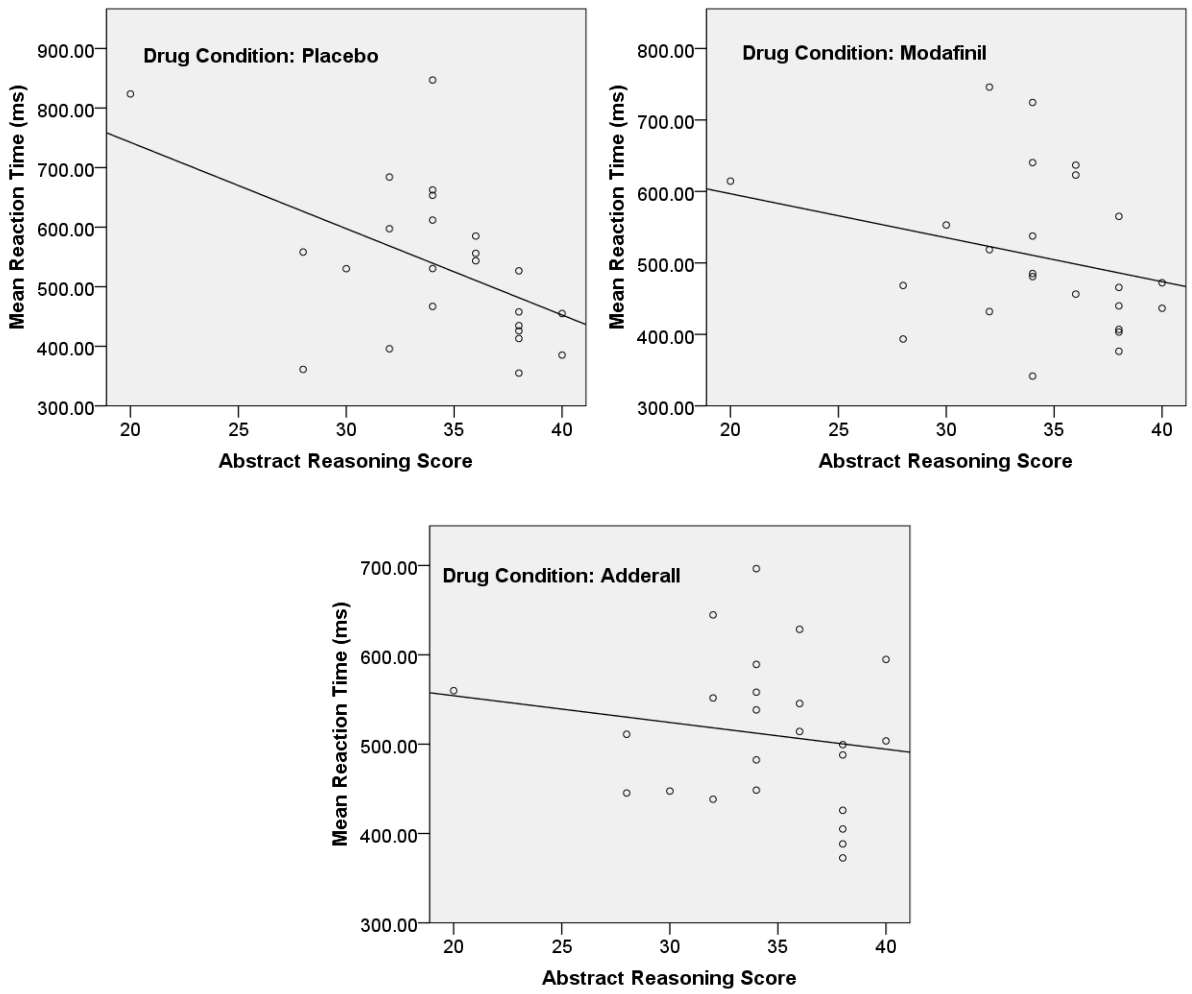

Figure 4. Relationship between mean reaction time on the RVIP (slow condition) and abstract reasoning score by drug.

Shifting attention test.

One participant's data was excluded due to an outlier. A one-way (drug: placebo, modafinil, MAS), repeated-measures MANCOVA with abstract reasoning score as the covariate was run to evaluate effects on reaction time and accuracy. No significant effects were found on accuracy. However, there was a significant interaction effect between drug condition and the covariate (abstract reasoning score) on reaction time, $F(2, 44) = 6.64$, $p = 0.003$. Figure 5 illustrates the relationship between the covariate and outcome variable for each drug condition. Planned contrasts show that reaction time was faster for MAS ($M = 1071.87$ ms, $SE = 37.66$) over that for placebo ($M = 1105.81$ ms, $SE = 34.39$); whereas that for modafinil (M = 1146.32 ms, $SE = 31.43$) did not differ from that for placebo. Finally, in order to further understand how the relationship between abstract reasoning and performance changed by drug condition, Pearson's r correlation coefficients were calculated. For placebo and modafinil conditions, the relationships were negative, however weak, $r(24) = -0.20$, $p = 0.35$ and $r(24) = -0.32$, $p = 0.13$. However, the relationship was stronger (mid-range) and negative in the MAS condition, $r(24) = -0.54$, $p = 0.007$.

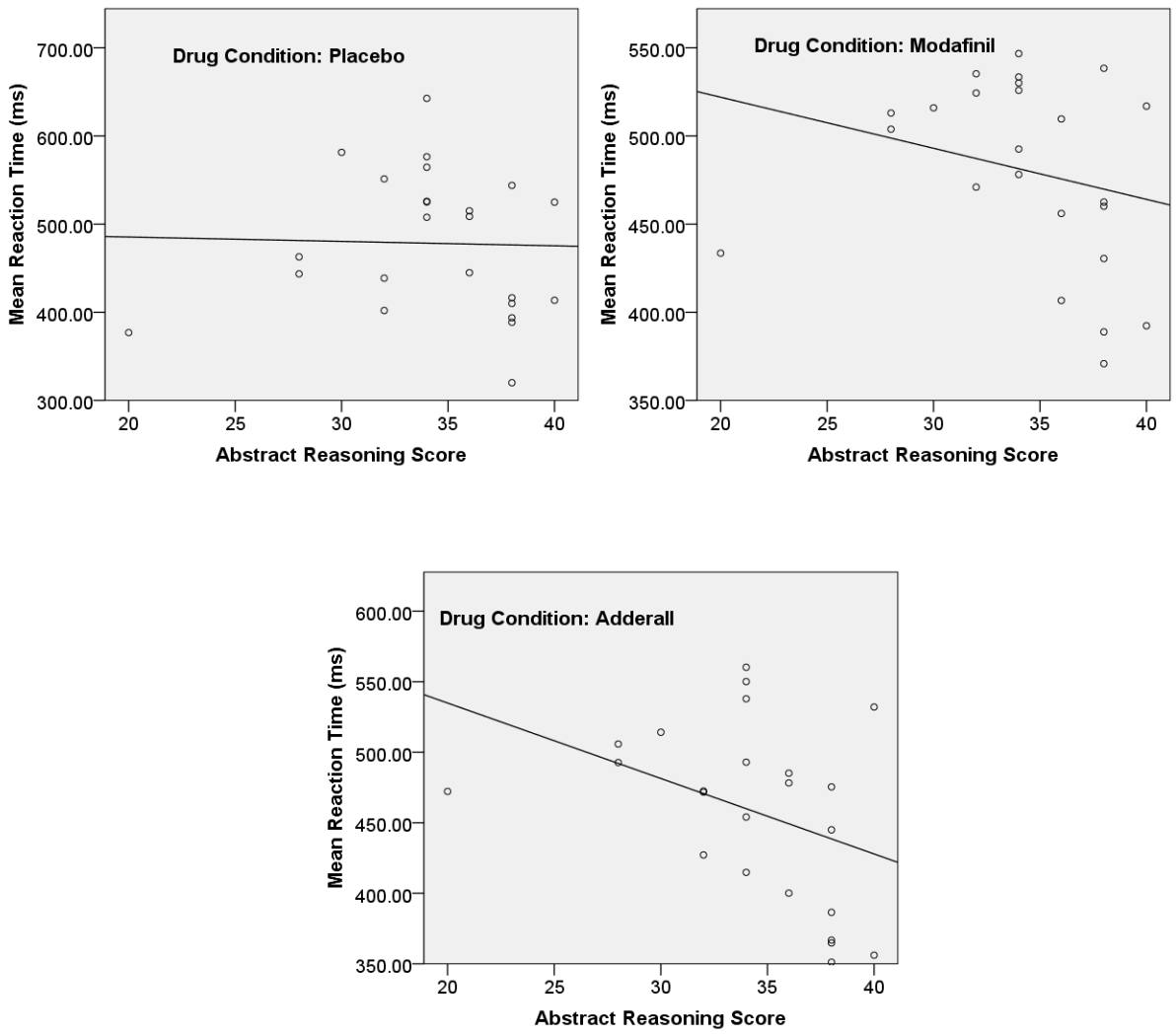

Figure 5. Relationship between mean reaction time on the shifting attention task and abstract reasoning score by drug.

Patrol exertion task.

The results of the ANCOVA did not support an effect of drug condition on reaction time, $F(2, 46) = 1.90$, $p = 0.16$.

Marksmanship task.

Five participants did not qualify on the baseline marksmanship task, 7 scored as ‘marksman’, 9 as ‘sharpshooter’, and 4 as ‘expert.’ A one-way (drug: placebo, modafinil, MAS), repeated-measures ANCOVA with abstract reasoning score as the covariate was run to evaluate effects on shot throughput (defined as shots per second). There was a significant interaction effect between drug condition and the covariate (abstract reasoning score) on throughput, $F(2, 46) = 6.64$, $p = 0.003$. Figure 6 illustrates the relationship between the covariate and outcome variable for each drug condition. Planned contrasts showed that throughput was greater for MAS ($M = 0.98$ shots/s, $SE = 0.01$) over that for placebo ($M = 0.95$ shots/s, $SE = 0.01$); whereas that

for modafinil (M = 0.94 shots/s, SE = 0.01) did not differ from that for placebo. Additionally, a separate ANCOVA was run to evaluate any effect on the number of misses. This analysis did not reach statistical significance, $F(2, 46) = 2.55$, $p = 0.08$. Finally, in order to further understand how the relationship between abstract reasoning and performance changed by drug condition, Pearson's r correlation coefficients were calculated. For placebo and modafinil conditions, the relationships were positive, however weak, $r(25) = 0.12$, $p = 0.57$ and $r(25) = 0.11$, $p = 0.60$. However, the relationship was slightly stronger and negative in the MAS condition, $r(25) = -0.36$, $p = 0.08$.

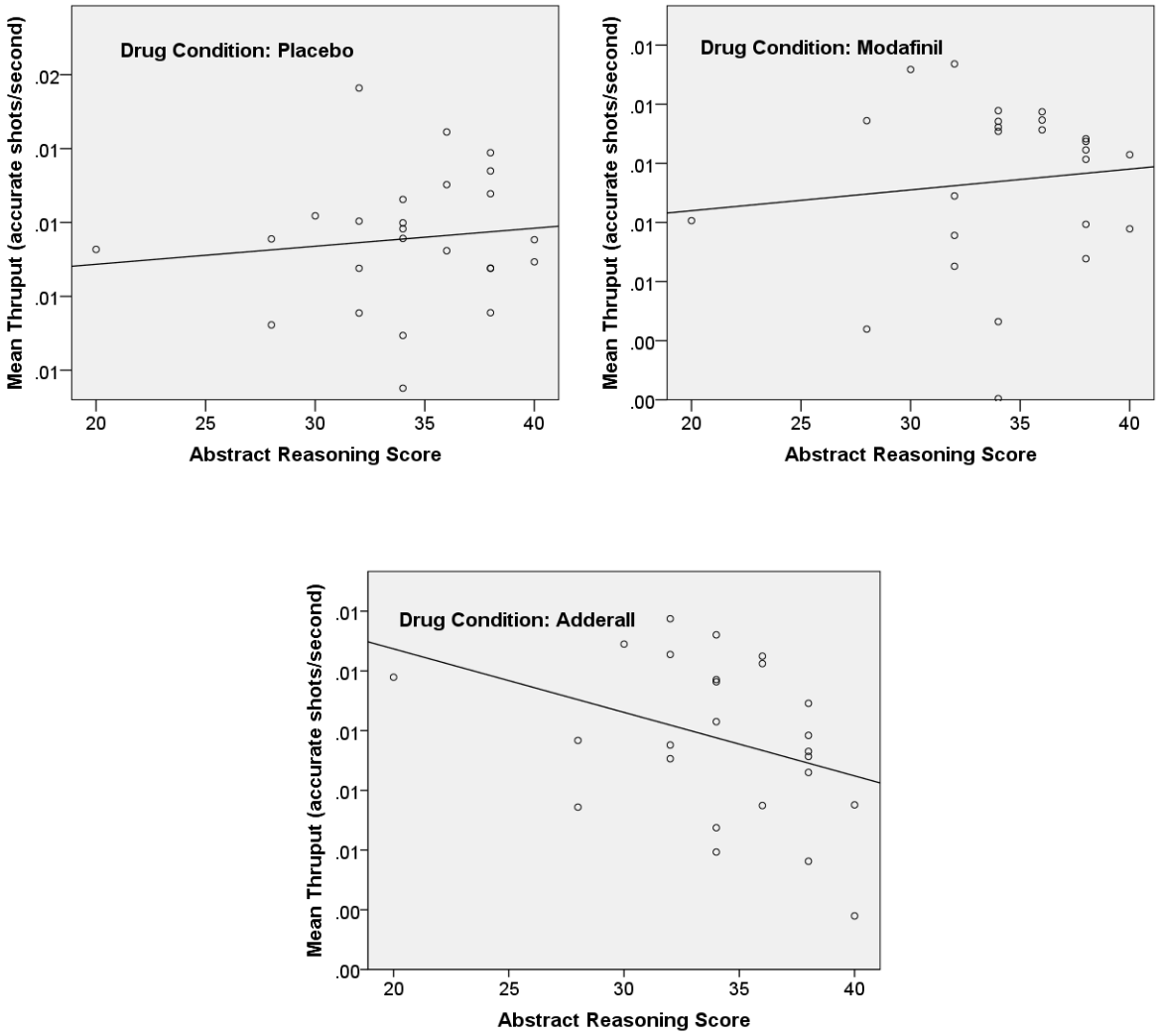

Figure 6. Relationship between mean throughput on the marksmanship task and abstract reasoning score by drug.

Objective 2

Stop signal test.

The result of the MANCOVA did not yield any significant effect of drug on mean percent correct, $F(2, 46) = 2.38$, $p = 0.10$, or reaction time, $F(2, 46) = 0.80$, $p = 0.45$.

Continuous performance test.

One outlier was removed from the analysis (n = 24). The result of the MANCOVA did not yield any significant effect of drug on accuracy, $F(2, 44) = 0.06$, $p = 0.94$, or reaction time, $F(2, 36) = 2.26$, $p = 0.12$.

Profile of mood states.

All seven subscales (tension, anger, fatigue, depression, confusion, vigor, esteem-related affect) were included as outcome measures in a one-way (drug: placebo, modafinil, MAS), repeated-measures MANOVA. There was a significant effect of drug on the fatigue subscale, $F(2, 40) = 3.59$, $p = 0.03$. Planned contrasts showed that fatigue was significantly less for MAS (M = -0.24, SE = 0.19) than that for placebo (M = 0.62, SE = 0.31); whereas that for modafinil (M = 0.19, SE = 0.20) did not differ from that for placebo. Fatigue scores decreased from pre- to post-testing for the MAS condition whereas fatigue increased for the placebo and modafinil conditions.

Evaluation of risk scale.

Two participants were excluded due to missing data. The one-way (drug: placebo, modafinil, MAS), repeated-measures MANOVA showed a significant drug effect on one subscale, *danger-seeking*, $F(2, 48) = 3.32$, $p = 0.04$. Post-hoc pairwise comparisons showed that *danger-seeking* scores were greater ($p = 0.01$) for the MAS condition (M = 49.31, SE = 2.62) than the modafinil condition (M = 45.62, SE = 2.78). The placebo condition (M = 47.15, SE = 2.76) did not significantly differ from either drug condition.

Karolinksa sleepiness scale.

Five participants were excluded from this analysis for missing data. The one-way (drug: placebo, modafinil, MAS), repeated-measures ANOVA did not support any drug effect on sleepiness scores, $F(2, 38) = 1.64$, $p = 0.21$.

Symptom checklist.

The symptom checklist was administered at three time points: pre-dosing, during testing, and prior to release. Here we report the symptoms reported during testing given the pre-dosing and prior to release administrations were used to determine participant safety. Table 4 shows the frequency of each symptom reported by drug condition.

Table 4. Frequencies of Symptoms Reported by Drug Condition

Symptom	MAS	Modafinil	Placebo
Nervousness	0	0	0
Excitation	1	0	0
Feelings of	1	0	2

aggression			
Headache	1	4	3
Feelings of happiness or elation	2	7	2
Pain in abdomen or stomach area	0	0	0
Dry mouth	2	1	1
Pounding heart	0	0	0
Racing heartbeat	0	0	0
Tremor	0	0	0
Nausea	0	0	0
Jitteriness	1	1	1

Discussion

This study was designed to evaluate the cognitive and performance-enhancing effects of two pharmaceuticals (modafinil, MAS) in healthy, rested Soldiers whilst controlling for baseline intelligence (defined as abstract reasoning). Additionally, the study aimed to document whether, and if so, to what degree, the test articles yield undesirable side effects. The findings, overall, suggest that MAS enhances executive function and attention, which may translate to observed enhanced marksmanship performance. Abstract reasoning does appear to moderate these effects, however, it is difficult to draw firm conclusions given that the sample appears to be above average in terms of intelligence.

Modafinil was found to enhance performance on the RVIP, a measure of sustained attention. However, closer inspection of the data suggest that the effect is primarily driven by the participant with the lowest abstract reasoning score of the sample. Visual inspection of Figures 3 and 4 shows that mean reaction time for that participant decreases by approximately 200 ms in the modafinil condition compare to placebo, whereas a participating with an abstract reasoning score of 30 appears to decrease by approximately 50 ms. Removal of this data point, did not reserve the finding but did weaken the effect. This supports the idea that those with lower abstract reasoning ability may benefit from modafinil more than with higher ability. Modafinil did not enhance performance on any other task.

MAS enhanced performance on the shifting attention task, a measure of attention and executive function, and marksmanship throughput. Interestingly, the relationships between abstract reasoning score and performance was negatively correlated in each drug condition suggesting that performance was best (quicker reaction times) for higher performers. Visual inspection of the shifting attention task data reveals an unexpected pattern. While reaction times

quicken for those scoring low on abstract reasoning, this enhancement appears to be greater for those on the higher end of spectrum. This is counterintuitive and inconsistent with past research findings. This pattern may ultimately not be representative of the population and true effect (the sample size of this study aligns with that notion) but further evaluation is needed to understand the true main and moderation effects. Overall, enhancement on this task aligns with the findings of Advokat (2010).

The results of marksmanship performance suggest that MAS enhanced throughput whereas placebo and modafinil did not. The interaction effect of abstract reasoning and drug is unique in that the direction of the relationship between the two variables is different for the MAS condition from that for the modafinil and placebo conditions. Specifically, the relationship is *positive* in modafinil and placebo conditions and performance improves as abstract reasoning score increases. Alternatively, in the MAS condition, the relationship is *negative* and it appears that performance decreases as abstract reasoning scores increase. One possible explanation is that MAS did not enhance performance for high abstract reasoners but did so for lower reasoners, thus driving the change in relationship direction. In order to establish whether baseline marksmanship skill level impacted the results, the analyses were also run excluding those who did not qualify on the marksmanship task at baseline and the outcome was unaffected. The degree of improvement is approximately three percent, which may or may not be practically significant. One possibility for future research is to increase the dosage and introduce some dynamic marksmanship tasks to further evaluate this effect and whether it is of practical importance.

The second study objective was to document the extent to which any undesirable side effects resulted from either drug condition. Neither drug affected performance on the two response inhibition tests. No mood disturbances were apparent with the exception of a decrease in “fatigue” in the MAS condition (a positive, desirable outcome). Very few physical side effects (dry mouth, headache, jitteriness, feelings of aggression) were reported with either drug condition.). Less than eight percent of the participants reported any single symptom. However, MAS was associated with an increase in thrill-seeking, risk attitudes. If this effect is true, this side effect alone may outweigh in cost any benefit in performance enhancement.

Our study had several limitations worth noting. Specifically, the variability in baseline ability, especially with respect to intelligence or abstract reasoning, was problematic in that the sample was skewed towards above average individuals. In order to fully understand that role that baseline performance and ability play in moderating any enhancement effects, a wider range of intelligence levels will need to be represented in the sample. A possible solution is to include this measure in the inclusion criteria and implement quota sampling. An additional point to consider is the limited sample size and homogeneity of the group. Finally, the dosages chosen for this study are on the low end of a typical therapeutic dose and the effects detected may not be large enough for practical purposes.

While our findings did not result in specific, implementable recommendations, they did provide a more-focused direction for future investigations. Specifically, this study supported the need for continued research examining performance on functional tasks and military relevant outcomes. Future research would benefit from including tasks that require multitasking and physical/dynamic components. Future data collection efforts may also include additional time

points for assessments in order to determine whether dosing impacts sleep or performance on the subsequent day.

Conclusion

The results of this study suggest that MAS may be effective at enhancing functional performance in healthy, rested Soldiers. Specifically, performance on a standard marksmanship qualification task improved following MAS administration over placebo. Performance was defined as accurate shots per second and this result suggests that shots were fired quicker without sacrificing accuracy.

The study results, overall, do not provide support for 200 mg of modafinil enhancing performance in healthy, rested Soldiers. However, modafinil did enhance sustained attention on one task, an effect largely driven by the participant with the lowest abstract reasoning score of the sample.

Abstract reasoning scores (used here as a proxy variable of intelligence) was related to performance and that relationship was differentially affected by condition.

The undesirable side effects seen with MAS included a change in risk-taking attitudes, specifically, a propensity towards thrill-seeking, and physical symptoms (dry mouth, headache, jitteriness, feelings of aggression). However, these physical symptoms were very rare (less than eight percent reported any single symptom).

References

Advokat, C. (2010). What are the cognitive effects of stimulant medications? Emphasis on adults with attention-deficit/hyperactivity disorder (ADHD). *Neuroscience and Biobehavioral Reviews, 34,* 1256-1266. doi: 10.1016/j.neubiorev.2010.03.006

American Psychiatric Assocation. (2000). Diagnostic and statistical manual of mental disorders, version IV. American Psychiatric Association.

Anthony, D. (2006). *EST 2000: Engagement Skills Trainer*. Cubic Defense Application.

Bagot, K. S., & Kaminer, Y. (2013). Efficacy of stimulants for cognitive enhancement in non-attention deficit hyperactivity disorder youth: A systematic review. *Addiction, 109,* 547-557. doi:10.1111/add.12460

Bakan, P. (1959). Extraversion-introversion and improvement in an auditory vigilance task. *British Journal of Psychology, 50*(4), 325-332.

Ballard, M. E., Gallo, D. A., & de Wit, H. (2014). Amphetamine increases errors during episodic memory retrieval. *Journal of Clinical Psychopharmacology, 34*(1), 85-92. doi:10.1097/JCP.0000000000000039

Baranski, J. V., Pigeau, R., Dinich, P., & Jacobs, I. (2004). Effects of modafinil on cognitive and meta-cognitive performance. *Human Psychopharmacology: Clinical and Experimental, 19*(5), 323-332.

Battleday, R. M. & Brem, A. K. (2015). Modafinil for cognitive neuroenhancement in healthy non-sleep deprived subjects: a systematic review. *European Neuropsychopharmacology, 25,* 1865-1881. doi: 10.1016/j.euroneuro.2015.07.028

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). Beck depression inventory-II. *Psychological Assessments, 78*(2), 490-8.

Conners, C. K., & Sitarenios, G. (2011). Conners' continuous performance test (CPT). In *Encyclopedia of clinical neuropsychology* (pp. 681-683). Springer.

Cope, Z. A., Minassian, A., Kreitner, D., MacQueen, D. A., Milinenne-Petiot, M., Geyer, M. A., Perry, W., & Young, J. W. (2017). Modafinil improves attentional performance in healthy, non-sleep deprived humans at doses not inducing hyperarousal across species. *Neuropharmacology, 125,* 254-262. doi: 10.1016/j.neuropharm.2017.07.031

Cropsey, K. L., Sciavon, S., Hendricks, P. S., Froelich, M., Lentowicz, I., & Fargason, R. Mixed-amphetamine salts expectancies among college students: Is stimulant induced cognitive enhancement a placebo effect? *Drug and Alcohol Dependence, 178,* 302-309. doi:10.1016/j.drugalcdep.2017.05.024

Curran, S. L., Andrykowski, M. A., & Studts, J. L. (1995). Short form of the Profile of Mood States (POMS-SF): Psychometric information. *Psychological assessment, 7*(1), 80.

Estrada, A., Kelley, A. M., Webb, C. M., Athy, J. R., & Crowley, J. S. (2012). Modafinil as a replacement for dextroamphetamine for sustaining alertness in military helicopter pilots. *Aviation, Space, and Environmental Medicine, 83*(6), 556-564. doi: 10.1037/t09699-0

Finke, K., Dodds, C. M., Bublak, P., Regenthal, R., Baumann, F., Manly, T., & Müller, U. (2010). Effects of modafinil and methylphenidate on visual attention capacity: A TVA-based study. *Psychopharmacology, 210*, 317-329. doi: 10.1007/s00213-010-1823-x

Farah, M., Haimm, C., Sankoorikal, G., & Chatterjee, A. (2009). When we enhance cognition, do we sacrifice creativity? A preliminary study. *Psychopharmacology, 202*, 541-547. doi:10.1007/s00213-008-1369-3

Franke, A. G., Gränsmark, P., Agricola, A., Schühle, K., Rommell, T., Sebastian, A., Ballo, H. E., Gorbulev, S., Gerdes, C., Frank, B., Ruckes, C., Tuscher, O., & Lieb, K. (2017). Methylphenidate, modafinil, and caffeine for cognitive enhancement in chess: A double-blind, randomized controlled trial. *European Neuropsychopharmacology, 27*, 248-260. doi:10.1016/j.euroneuro.2017.01.006

Geng, J. J., Soosman, S., Sun, Y., DiQuattro, N. E., Stankevitch, B., & Minzenberg, M. J. (2013). A match made by modafinil: Probability matching in choice decisions and spatial attention. *Journal of Cognitive Neuroscience, 25*(5), 657-669. doi: 10.1162/jocn_a_00333

Gilleen, J., Michalopoulou, P. G., Reichenberg, A., Drake, R., Wykes, T., Lewis, S. W., & Kapur, S. (2014). Modafinil combined with cognitive training is associated with improved learning in healthy volunteers: A randomised controlled trial. *European Neuropsychopharmacology, 24*, 529-539. doi: 10.1016/j.euroneuro.2014.01.001

Harnish, M. J., Beatty, W. W., Nixon, S. J., & Parsons, O. A. (1994). Performance by normal subjects on the Shipley Institute of Living Scale. *Journal of clinical psychology, 50*(6), 881-883.

Ilieva, I., Boland, J., & Farah, M. (2013). Objective and subjective enhancing effects of mixed amphetamine salts in healthy people. *Neuropharmacology, 64*, 496-505. doi:10.1016/j.neuropharm.2012.07.021

Kaida M, Takahashi T, Åkerstedt A, Nakata Y, Otsuka T, Haratani K, et al. (2006). Validation of the Karolinska sleepiness scale against performance and EEG variables. *Clinical Neurophysiology, 117*, 1574-81.

Kessler, R. C., Adler, L., Ames, M., Demler, O., Faraone, S., Hiripi, E. V. A., Howes, M.J., Jin, R., Secnik, K., Spencer, T., & Ustun, T. B. (2005). The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. *Psychological medicine, 35*(2), 245-256.

Logan, G. D., Schachar, R. J., & Tannock, R. (1997). Impulsivity and inhibitory control. *Psychological science*, *8*(1), 60-64.

Macleod, C. M. (1991). Research on the Stroop effect: an integrative review. *Psychological Bulletin*, *109*(2), 163–203.

Makris, A. P., Rush, C. R., Frederich, R. C., Taylor, A. C., & Kelly, T. H. (2007). Behavioral and subjective effects of d-amphetamine and modafinil in healthy adults. *Experimental and Clinical Psychopharmacology*, *15*(2), 123.

Marchant, N. L., Kamel, F., Echlin, K., Grice, J., Lewis, M., & Rusted, J. M. (2009). Modafinil improves rapid shifts of attention. *Psychopharmacology*, *202*(1), 487-495.

Matthews, T.D., Orzech, J.A., & Lasssiter, K.S. (2011). Does the Shipley Institute of Living Scale measure fluid and crystallized abilities? North American Journal of Psychology, 13(2), 255-266.

McIntire, L. K., McKinley, R. A., Goodyear, C., & Nelson, J. (2014). A comparison of the effects of transcranial direct current stimulation and caffeine on vigilance and cognitive performance during extended wakefulness. *Brain stimulation*, *7*(4), 499-507.

McNair, D. M., Lorr, M., & Droppleman, L. F. (1981). Profile of mood states, revised (POMS). *EdITS/Educational and Industrial Testing Service*.

Miller, G. (1956). The magical number seven, plus or minus two–the magical number seven, plus or minus two: some limits on our capacity for processing information. *Psychological Review, 63,* 81-97.

Mohamed, A. D. & Lewis, C. R. (2014). Modafinil increases the latency of response in the Hayling Sentence Completion Test in healthy volunteers: A randomised controlled trial. *PLOS ONE, 9*(11), e110639. doi: 10.1371/journal.pone.0110639

Monk, T. H., Buysse, D. J., Kennedy, K. S., Potts, J. M., DeGrazia, J. M., & Miewald, J. M. (2003). Measuring sleep habits without using a diary: the sleep timing questionnaire. *Sleep, 26*(2), 208-212.

Müller, U., Rowe, J. B., Rittman, T., Lewis, C., Robbins, T. W., & Sahakian, B. J. (2013). Effects of modafinil on non-verbal cognition, task enjoyment and creative thinking in healthy volunteers. *Neuropharmacology, 64*, 490-495. doi: 10.1016/j.neuropharm.2012.07.009

Nelson, J. M., McKinley, R. A., McIntire, L. K., Goodyear, C., & Walters, C. (2015). Augmenting visual search performance with transcranial direct current stimulation (tDCS). *Military Psychology*, *27*(6), 335-347. doi: 10.1037/mil0000085

Pringle, A., Browning, M., Parsons, E., Cowen, P. J., & Harmer, C. J. (2013). Early markers of cognitive enhancement: Developing an implicit measure of cognitive performance. *Psychopharmacology, 230,* 631-638.

Randall, D. C., Fleck, N. L., Shneerson, J. M., & File, S. E. (2004). The cognitive-enhancing properties of modafinil are limited in non-sleep-deprived middle-aged volunteers. *Pharmacology Biochemistry and Behavior, 77*(3), 547-555.

Royer, F. L. (1971). Information processing of visual figures in the digit symbol substitution task. *Journal of Experimental Psychology*, *87*(3), 335.

Samanez-Larkin, G., Buckholtz, J. W., Cowan, R. L., Woodward, N. D., Li, R., Ansari, M. S., … & Zald, D. H. (2013). *Biological Psychiatry, 74,* 99-105. doi: 10.1016/j.biopsych.2012.10.032

Scherer, M. R., Weightman, M. M., Radomski, M. V., Smith, L., Finkelstein, M., Cecchini, A., Heaton, K. J., & McCulloch, K. (2018). Measuring Soldier performance during the patrol-exertion multitask: preliminary validation of a postconcussive functional return-to-duty metric. *Archives of physical medicine and rehabilitation*, *99*(2), S79-S85.

Sicard, B., Jouve, E., & Blin, O. (2001). Risk propensity assessment in military special operations. *Military Medicine*, *166*(10), 871-874.

Theunissen, E. L., de la Asuncion Elvira, J., van den Bergh, D., & Ramaekers, J. G. (2009). Comparing the stimulant effects of the H1-antagonist fexofenadine with 2 psychostimulants, modafinil and methylphenidate. *Journal of clinical psychopharmacology*, *29*(5), 439-443.

Turner, D. C., Robbins, T. W., Clark, L., Aron, A. R., Dowson, J., & Sahakian, B. J. (2003). Cognitive enhancing effects of modafinil in healthy volunteers. *Psychopharmacology*, *165*(3), 260-269.

Weafer, J., Baggott, M. J., & de Wit, H. (2013). Test–retest reliability of behavioral measures of impulsive choice, impulsive action, and inattention. *Experimental and clinical psychopharmacology*, *21*(6), 475.

Zachary, R.A. (1986). *Shipley Institute of Living Scale: Revised manual*. Western Psychological Services.

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