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A DOUBLE-BLIND PLACEBO-CONTROLLED INVESTIGATION OF THE EFFICACY OF MODAFINIL FOR MAINTAINING ALERTNESS AND PERFORMANCE IN SUSTAINED MILITARY GROUND OPERATIONS

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14. ABSTRACT

Background: With the advent of the 24/7 warfighter, novel pharmaceutical agents have come to the forefront of interest for maintaining sustained operations. The eugregoric, modafinil, was administered during an 88-hr sleep loss study to evaluate its performance maintenance capability. ***Hypothesis:*** A modafinil dosing schedule (100/100/200 mg), would maintain cognitive and psychomotor performance at or near baseline levels throughout the experimental period. ***Methods:*** A repeated measures, double blind design was used to examine 100 and 200 mg doses of modafinil administered every eight hours to twelve participants. Cognitive and physiological tests were presented iteratively throughout the experimental sessions. ***Results/Conclusions:*** The results of this study provide some evidence that modafinil partially attenuates the performance decrement caused by sleep loss in field environments, thus increasing the likelihood of successful mission accomplishment. As anticipated, modafinil had very little impact upon physical performance, had no adverse physiologic effects, and produced few side effects. Modafinil may negatively impact sleep but the effect appears minimal and should be investigated in a controlled manner. The universal acceptance of modafinil by our participants, its observed mild performance advantages, and its low health risk, make it a candidate for field applications.

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Table of Contents

INTRODUCTION

It is well established that fatigue causes significant decrements in performance. In the aviation environment, performance decrements, especially on long-duration missions, may lead to untoward outcomes ranging from severe crew discomfort, to mission degradation, to loss of an aircraft and its crew. Present Air Force operations require long-duration missions to happen more frequently than in the past. Use of conservative fatigue countermeasures may prove insufficient to counter the effects of extremely long-duration missions. Dextroamphetamine has a good track record in countering fatigue, but has some potentially significant undesirable side effects (e.g., agitation, inability to nap, addiction, etc). Modafinil has been extensively studied in the aviation environment and appears to be effective at significantly extending performance during conditions of sleep-loss without the risk of significant unwanted side effects.

Modafinil was developed and brought to the market about 15 years ago by the L Lafon Laboratory of France. Initial studies in animals and humans delineated effective levels of wakefulness and psychomotor performance which were maintained by well tolerated doses of the medication (Bensimon, Benoit, Lacomblez, and Weiler 1991). Multiple studies performed since then support these findings. In 1998, the pharmaceutical company Cephalon received FDA approval to market this new vigilance-enhancing drug, modafinil (Provigil®), for the management of narcolepsy. Modafinil is also approved to treat excessive daytime sleepiness brought about by obstructive sleep apnea/hypopnea syndrome. In January, 2004, modafinil was approved by the FDA to treat sleepiness associated with chronic shift work sleep disorder.

This drug belongs to a new group of drugs called "eugregorics". Eugregorics mimic the effects of amphetamines by producing high quality wakefulness, but lack the typical negative side effects associated with amphetamines (Lagarde, Batéjat, Van Beers, Sarafian, and Pradella, 1995). The neuro-chemical mechanism of modafinil is not yet fully understood, but modafinil is known to affect the alpha-1 adrenergic receptors, akin to the neurotransmitter norepinephrine. Modafinil does not work by inhibiting reuptake; instead it directly stimulates the norepinephrine receptors (Cephalon, 1998). Lin, Hou, Rambert, and Jouvet (1997) found modafinil both chemically and pharmacologically different from amphetamines in that modafinil produces long lasting waking effects without behavioral modification, addictive attributes, or sleep rebound. In addition to its lack of adverse effects, modafinil exhibits a terminal half-life of 9-14 hrs with peak blood concentrations 2-4 hrs after absorption with an oral clearance of 50-60 mL/min (Wong, Gorman, McCormick, & Grebow, 1997). This profile makes modafinil a prime candidate for operational use in situations requiring sustained wakefulness. In summary, the efficacy of modafinil to reduce sleep-loss induced performance decrements has been proven. Likewise, the clinical safety of modafinil has also been proven (Morehouse, Broughton, Fleming, George, and Hill, 1997; Eddy, Gibbons, Miller, Storm, French, Stevens, Barton, Cardenas, and Hickey, 2005).

Research into possible unfavorable side effects of modafinil (Morehouse, Broughton, Fleming, George, and Hill, 1997) found subjects reported 52 adverse effects, yet none were statistically different from the placebo group. Phase 3 clinical trials have confirmed that the only adverse effect more frequent in the 400 mg/day group was headache. Doses of 800 mg/day produced elevations in blood pressure and pulse rate. Pigeau, Naitoh, Buguet, McCann, Baranski, Taylor,

Thompson, & Mack (1995) reported an increased frequency of urination when compared to Dextroamphetamine or placebo. Caldwell and Caldwell (2000) reported anecdotal evidence of increased vestibular complaints (i.e. dizziness) in a study involving three 200 mg doses given at 4-hr intervals. An evaluation of this phenomenon conducted by Eddy, et al, (2005) and performed at Brooks AFB, TX showed no negative vestibular effects associated with a single 400 mg dose of modafinil.

The total dosage of modafinil used in this study was 400 mg/day given as 100 mg every 8 hours except for 200 mg given before the expected nighttime circadian low. This dose schedule was consistent with prior studies. Several of these studies (Bensimon, Benoit, Lacomblez, Weiller, Warot, Weial and Puech, 1991; Lagarde and Batejat, 1995; Batéjat and Lagarde, 1999) clearly demonstrated that 200 mg of modafinil administered either in a single dose or repeated every 8-hrs for longer periods of arousal significantly enhanced performance during periods of sleep deprivation. More recent investigations have focused on the effectiveness of 100 mg doses. In a study by Baranski, Cian, Esquivie, Pigeau, & Raphel (1998), subjects given a dosage of 100 mg every eight hours, over a 24-hour period, maintained cognitive performance levels throughout 64 hours of sleep deprivation. Subjects in the same study, given 50 mg every eight hours, over a 24-hour period, maintained non-significant performance improvement when compared to placebo. Stivalet, Esquivie, and Barraud (1998) studied the effects of modafinil on attention processing during 60 hours of sleep deprivation. Subjects were given a total of 300 mg/day in 100 mg doses every 8 hours. Results indicated that modafinil prevented both slowing of serial processing and the normal increases in the rate of error during the period of sleep deprivation. A recent study performed at Brooks City-Base by Whitmore, Fischer, Hickey, Cardenas, Heintz, Scoggins (2004) kept participants awake for 88-hrs while they received either 100 mg or 200 mg every 8 hours (nine total doses). Few side effects were observed in the study and performance was relatively well maintained through 3 days and 2 nights of sleep deprivation (approximately the first 60-hrs). Performance for both conditions was better than that under a no-drug condition; however, both conditions suffered significant performance degradation on the third night of sleep-loss.

The purpose of this study, done at the request of the operational military community, was to use field conditions to assess ground air controller and medical personnel's ability to perform operationally related tasks with and without the use of modafinil in a sleep-deprived setting. This study was designed to include elements of field activities in a sleep-loss setting chosen to simulate some of what sustained Special Forces personnel experience in an operational environment. Based on the previous research, modafinil should be well suited to moderate performance in this environment given its performance enhancing abilities, its relatively low incidence of side effects, and its overall reduced risk (modafinil is a schedule IV controlled substance versus dextroamphetamine which is a schedule II).

METHODS

This was a double-blind placebo-controlled cross-over study. We recruited 12 male advanced special tactics military personnel, ages 24 – 37yrs; six trained in the field of medical rescue and six trained in combat control. All participants were volunteers and gave written informed

consent. The protocol was approved by the Institutional Review Board (FBR-2004-40-H). Prior to the study each participant underwent a medical evaluation to ensure fitness to participate in the study. All participants were ground tested with modafinil prior to their participation in the study.

Primary data collection occurred over two separate 72 hour experimental sessions during which multiple performance tests and operational tasks were given. The two sessions were separated by 5 days. All volunteers participated in both sessions, receiving modafinil in one session and identical placebo tablets in the other, at the times and doses indicated in the experimental schedule (Table 1). Order of drug administration was randomly assigned and balanced.

Time	Day 1	Day 2	Day 3	Day 4
0000	Pre-event Sleep	100 mg Dose	200 mg Dose	200 mg Dose
0100		NAV Course	NAV Course	NAV Course
0200				
0300				
0400		Comm Tasks	Comm Tasks/AFRL (PVT)	Comm Tasks
0500		AFRL (PVT)	Live Fire	AFRL (PVT)
0600		Meal	Meal	Meal
0700	AFRL Practice	100 mg Dose at 0715	100 mg Dose at 0715	Live Fire
0800	Marksmanship Practice	Live Fire	Nap 0820 - 1020	
0900	Live Fire Practice			AFRL Test (no jump)
1000				Surveys
1100	AFRL Test	AFRL Test	AFRL Test (no jump)	End of study
1200	ATC/Medical	ATC/Medical	ATC/Medical	
1300	Obstacle Course	Obstacle Course	Obstacle Course	
1400	Meal	Meal	Meal	
1500	Marksmanship	100 mg Dose	100 mg Dose	
1600	AFRL (2 work scales,	AFRL (2 work scales,	AFRL (2 work scales,	
1700	PVT)	PVT)	PVT)	
1800	Stan/Eval	Stan/Eval	Stan/Eval	
1900				
2000	Meal	Meal	Meal	
2100	Skills Test	Skills Test	Skills Test	
2200				
2300	AFRL Test	AFRL Test (no jump)	AFRL Test (no jump)	

Table 1: Experimental Design Schedule. NAV: Navigation course; AFRL Test includes: cognitive performance tests; jump task and subjective measures; ATC: Air Traffic Control task; Comm: radio setup task

Experimental testing consisted of two simple cognitive tests (mathematical processing and grammatical reasoning) performed on a laptop computer, a simple 10-min un-alerted reaction time task (PVT), a subjective sleepiness check, a fatigue questionnaire, a mood questionnaire, a symptom survey/health check, a standing jump task, and a blood pressure/heart rate check. Prior to the start of data collection, two 2-hr training sessions were conducted. During these orientation and training periods participants were trained to asymptotic performance on all performance tests. Each participant was assigned a randomized participant number under which his data was recorded so as to maintain anonymity. Objective identification of sleep/wake patterns was achieved with the use of individual actigraphs attached to each participant's wrist.

Description of measures

Cognitive Tests

Cognitive Performance Battery (Automated Neuropsychological Assessment Metrics - ANAM) - The battery required about 6 minutes to complete (divided equally between the two following

tests): Mathematical Processing Test - presented simple addition and subtraction problems containing two operands. Grammatical Reasoning Test - participants answered whether two statements accurately described the relational order of three symbols. Mean reaction time for correct responses (MRTC), accuracy, throughput, standard deviation of correct response time (SDRTC), and lapses were recorded for both tests.

Psychomotor Vigilance Task – This 10-min task was a simple un-alerted reaction time test. Mean reciprocal reaction time (MRRT - the number of responses per second of response time), lapses, and the standard deviation of MRRT were analyzed.

Field Tasks
Air Traffic Control Task – The six participants trained in combat control performed an ATC task which involved managing aircraft at a forward deployed airfield. A composite score was calculated from a matrix of critical scenario factors.

Medical Task – The six participants trained in medical rescue performed an emergency medical treatment task. Subjective observations were the primary outcome of this task and specific comments are included in the paper. No other analysis was performed.

Navigation Course – Participants walked a navigation course which required approximately 1-hr to complete. This data set was incomplete, and will not be presented.

Live Fire – Following a firing warm-up each day, participants were scored on accuracy when firing 40 rounds at targets 50 meters in distance.

Exertion surveys – a mental exertion survey and a physical exertion survey were given each day to assess participants' perceived exertion levels for the field tests.

Physical Measures
Standing Jump Task – Participants performed two sets of 20 vertical jumps each. Jumping was performed in place; jump height, average work, and average power were recorded.

Obstacle Course – Participants performed 15 obstacles which challenged their strength, balance, and endurance. Total time to completion was used as the measure.

Fitness Tasks – Included 3 mile run, 1500 meter swim, push-ups, pull-ups and sit-ups. Times to completion were recorded for the aerobic tasks while counts were recorded for the anaerobic tasks.

Physiologic Measures
Activity Monitoring –An actigraph, a wristwatch like device containing accelerometers, and an activity log were used to identify/record participant sleep/wake patterns for three days prior to each testing session, during the Day 3 nap, and for three days following each test session.

Vitals – Heart rate, blood pressure, and oral temperature were measured during every AFRL Test block.

Subjective Measures

Symptom Questionnaire – Participants responded to a list of 45 symptoms, and recorded the presence and severity (none, slight, moderate, severe) of any experienced during that test block.

Profile of Mood States – Subjective affect was sampled using the POMS paper-and-pencil survey. The POMS consists of sixty-five adjectives, grouped into six sub-scales, describing feeling and mood.

Subjective Sleepiness Scale – Participants rated their sleepiness on a 7 point Likert scale, where 1 was "not sleepy at all" and 7 was "unable to remain awake".

Physical / Mental Exertion – Physical exertion was measured using a fifteen point scale ranging from 6-no exertion to 20-maximal exertion. Mental exertion was measured using a seven point scale ranging from 1-nothing to do to 7-overloaded

Data Analysis: For each outcome variable, a repeated measures analysis of variance (ANOVA), with two within-subjects factors (drug and time) was performed to test whether changes occurred over time, and to determine whether the magnitudes of the changes were drug dependent (i.e., drug by time interaction). For the AFRL measures, only the 1600 and 0400 times (high and low points of the circadian cycle) were included in the analysis. For other measures (e.g., physical performance), all available time points were used. Post-hoc analysis was accomplished using one-tailed Student's t-tests to compare the placebo and drug conditions at each time point, separately. *Statistical Power:* Sample size was determined based on the post-hoc comparisons of the two drug conditions at specific time points. The sample of 12 participants provided an 83% chance (power) of detecting differences that were about 8/10ths of a standard deviation in magnitude (Effect Size = 0.8), when testing at the 0.05 one-tailed alpha level.

RESULTS

All 12 participants completed the study. However, due to a pre-existing physical injury, one participant was unable to complete some of the physical testing measures. Any mention of statistical significance refers to an alpha level of .05. Appendices A, B, and C, contain the descriptive statistics and statistical test results for all of the cognitive, physical, and subjective measures recorded in this study. For each outcome measure, the baseline mean and standard deviation are shown followed by the mean (and standard deviation) from each subsequent time point. The ANOVA results are shown in the last three columns of the table. For those variables where the ANOVA indicated significant drug or drug by time effects, superscripts (defined in the table legend) are used to identify significant post-hoc results.

Cognitive Measures

Math Processing

Significant time main effects were observed for lapses, mean reaction time correct, standard deviation of correct response time, accuracy, and throughput. Generally, performance decreased over the duration of the study, with the largest effects occurring at the circadian nadirs. In addition, a significant drug effect was observed for the accuracy measure. Post hoc testing

revealed the modafinil condition led to significantly higher accuracy at day 2-0400, and day 3-0400 (see Figure 1). There were no drug by time effects.

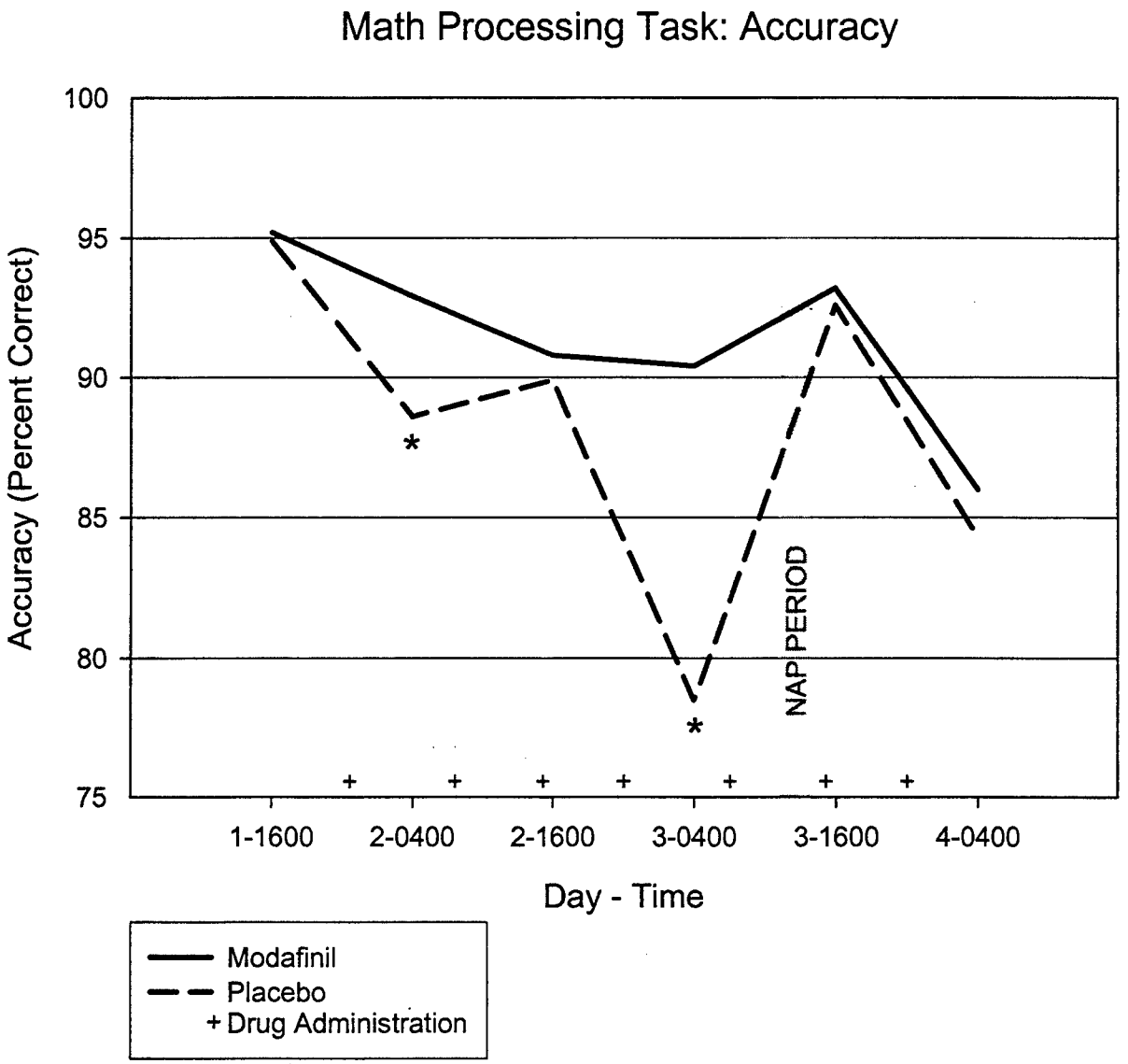

Figure 1
Changes in accuracy across the four days of testing under placebo and modafinil conditions
* indicates significant drug differences $p \leq .05$

Grammatical Reasoning

It should be noted that the second week of data from the Grammatical Reasoning test was lost due to a software failure; therefore we were limited to a between-groups analysis (n=6/condition). All measures for this task (accuracy, percent lapses, mean response time correct, standard deviation of the correct response time, and throughput) demonstrated a significant decrease in performance over time. There were no drug or drug by time effects.

Psychomotor Vigilance Task

Significant main effect decreases in performance were observed over time for lapses, mean reciprocal response time, and standard deviation of the reciprocal response time. There were no drug or drug by time effects.

Physical Performance Measures

Jump Test

Average jump height revealed significant time and drug main effects; however, post hoc tests for drug differences did not show a difference at any specific point (see Figure 2). Average work performed showed a significant decrease over time while average jump power contained no significant findings. There were no significant drug by time effects for any measure.

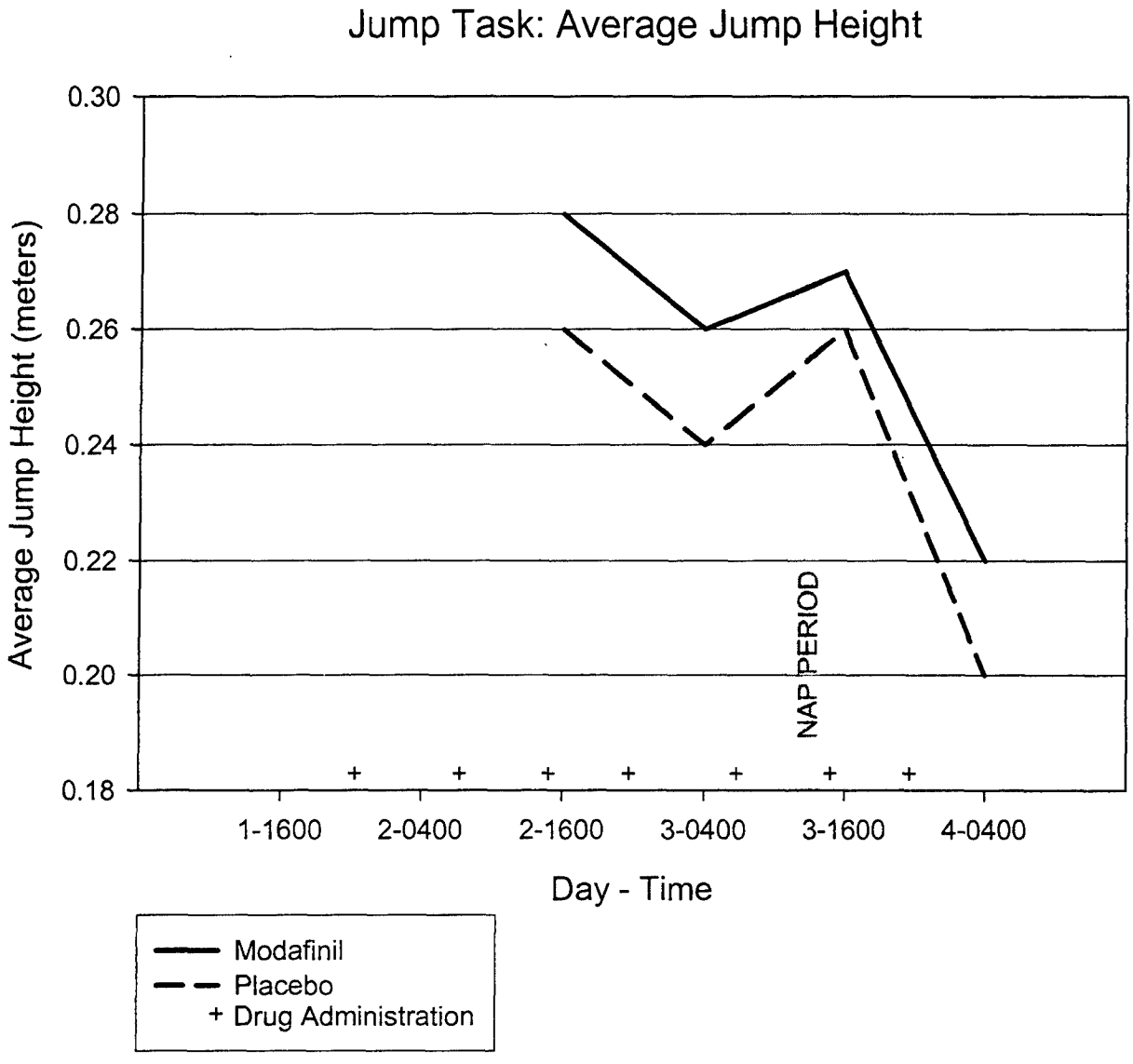

Figure 2
Changes in mean jump height across the four days of testing under placebo and modafinil conditions.

Live Fire

No significant changes were observed for this task.

Obstacle Course

No significant changes were observed for this task.

Standard Fitness Evaluation

The number of pull-ups performed demonstrated a significant time main effect, but no drug or drug by time effects. The 1.5 mile split time, the 3 mile total run time, number of push ups, number of sit-ups, and the 1500 meter swim time contained no significant findings.

Physiological Measures

Heart Rate

Overall, HR significantly decreased over time, but no drug or drug by time effect was detected.

Blood Pressure

No significant effects were observed for this measure.

Temperature

A time effect was present in these data, but no drug or drug by time effects were detected.

Nap Actigraphy and Subjective Nap Survey

Based on the actigraph results, mean activity was significantly higher, and total sleep time was significantly lower under modafinil as compared to placebo (see Figure 3). The subjective survey mirrored the actigraph results; total sleep length was significantly less under modafinil, and the quality of sleep rating approached significance.

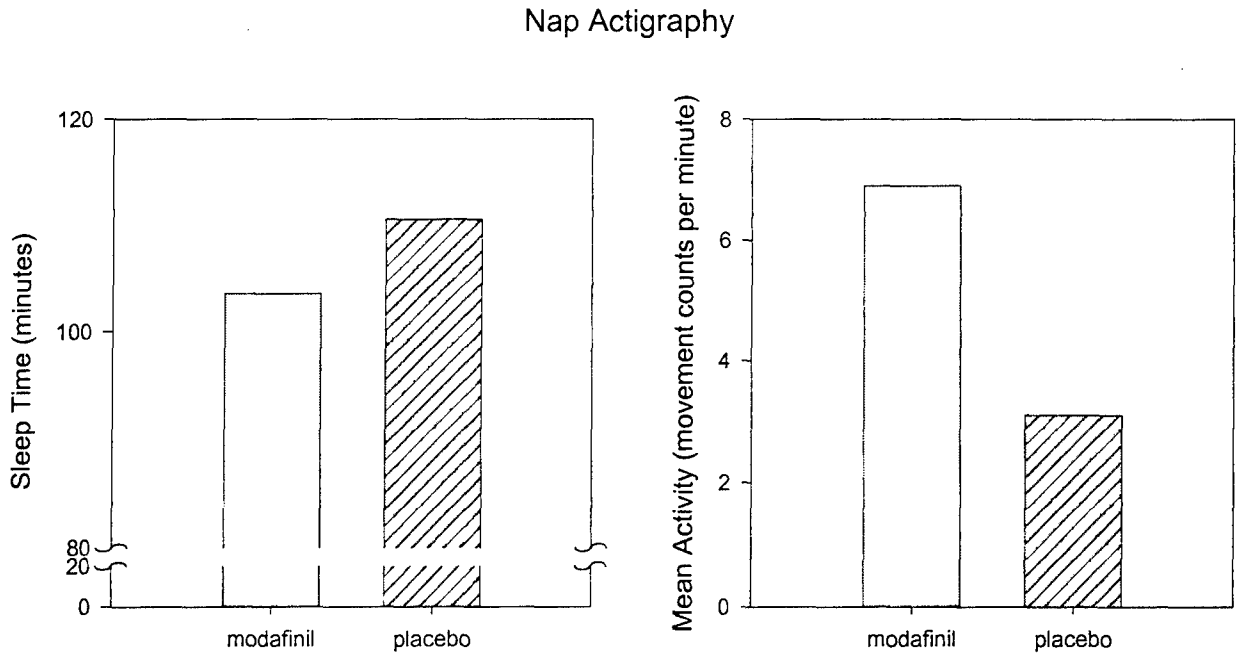

Figure 3
Comparison of sleep characteristics under modafinil and placebo.
A significant drug effect was found ($p \leq .05$) for both total sleep time and activity count.

Subjective Measures

Profile of Mood States

The anger, depression and tension scales did not show any significant changes whereas confusion and fatigue ratings increased significantly over time. The vigor scale yielded significant time and drug main effects, and subsequent post hoc testing identified the modafinil condition as having a higher level of vigor on day 3-0400 and day 3-1600 (see Figure 4).

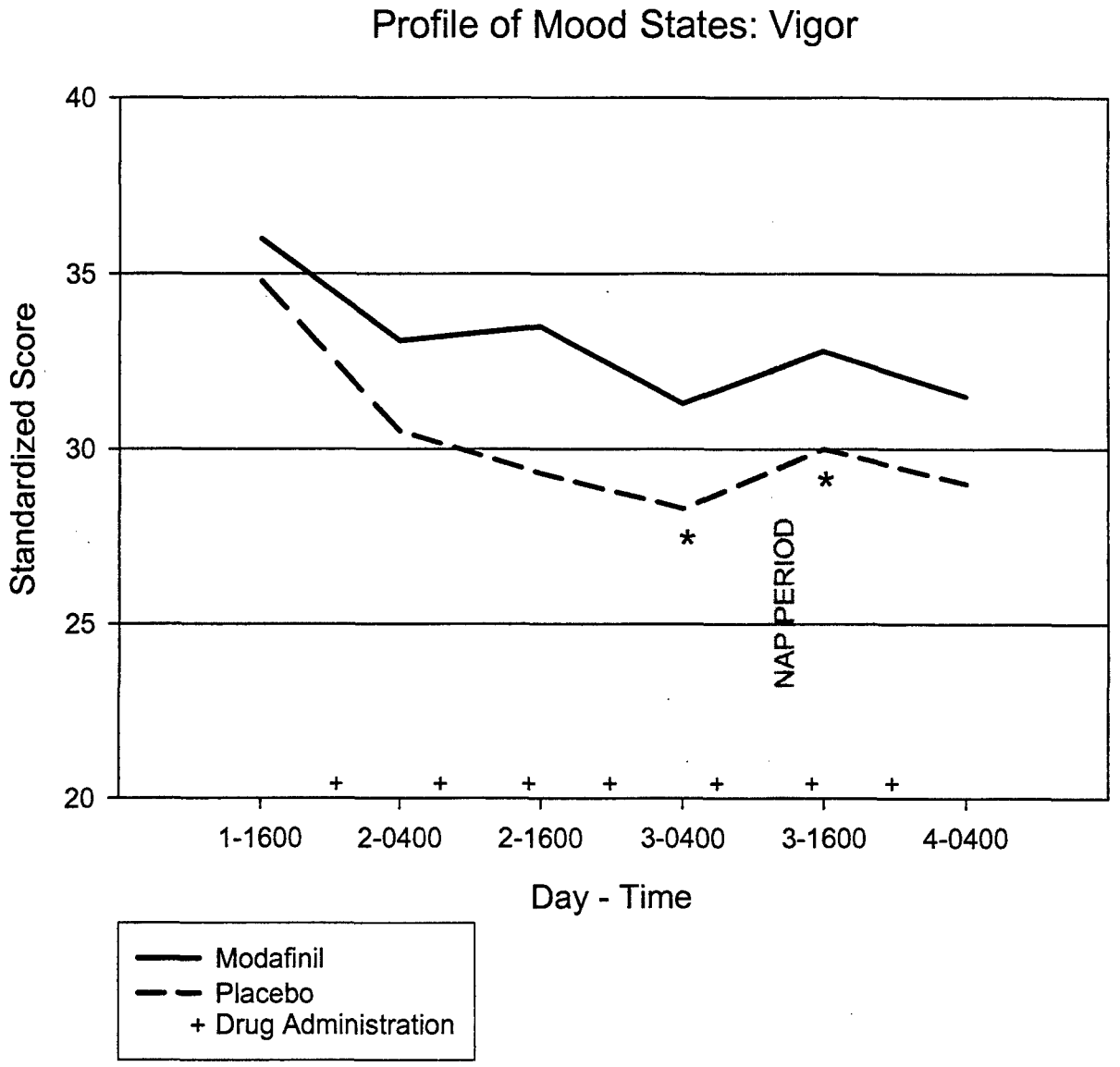

Figure 4
Changes in standardized mood score across the four days of testing under placebo and modafinil conditions.
* indicates significant drug differences $p \leq 0.05$

Stanford Sleepiness Score

There was a significant increase in sleepiness ratings over time. No drug effects were detected.

Physical Exertion Scale

There was a significant increase in the physical exertion ratings over time. No drug effects were detected.

Mental Exertion Scale

No significant effects were observed for this measure.

Subjective Symptoms

The side effects reported during this study were minimal. Table 2 shows details for the two symptoms that were noteworthy. There was not a statistical difference between the modafinil and placebo conditions for either symptom.

Severity Score	Headache		Nausea	
	Modafinil	Placebo	Modafinil	Placebo
1- None	5	9	8	11
2- Slight	5	1	2	1
3-4 Moderate To Severe	2	2	2	0

Table 2: Most frequently reported side effects. Counts are based on the maximum score reported over the duration of the study.

DISCUSSION

Modafinil has been shown in the literature to be effective at attenuating performance decrements typically seen with sleep deprivation. This study provides support that this effect may also apply in field settings. Cognitive performance as noted by math accuracy was significantly improved in the modafinil group as compared to the placebo group in the early morning circadian-low period of days 2 and 3. While not statistically significant, a nearly identical trend was seen for math throughput (During the circadian nadir of both days 2 and 3, 9 of 12 (75%) participants had higher throughputs under modafinil). Significant subjective improvement under modafinil, as compared to placebo, was seen for the Vigor portion of the POMS toward the end of the study. No other measures indicated a significant modafinil advantage. Similar low magnitude effects were observed in a previous field study (Whitmore, Doan, Fischer, French, Heintz, Hickey, Hurtle, Kisner, and Smith, 2004).

The dosing scheme used in the current study was similar to schemes recommended by Buguet, Moroz, & Radomski (2003). However, Buguet et al. also recommended a 2-hr sleep period each day. Our dosing regimen was too low to obviate the majority of performance decrements brought about from complete sleep loss. We constrained our dosing schedule to meet the maximum daily dosage of 400mg approved by the Air Force Surgeon General (2 Dec 2003, USAF, Headquarters). Increasing the dosing would likely lead to increased reporting of adverse symptoms. However, there may be some room to alter or increase the dosing regimen (e.g., 100mg every 6hrs or 200mg every 8/hrs) which might increase performance without drastically increasing side effects.

The participants in the present research probably differed from the participant samples used in many previous laboratory studies. Our participants were highly trained, motivated, and selected individuals who may have been more fatigue resistant than a normal population. Our participants were allowed to spend the duration of the study (except for the cognitive performance testing) in a group, often providing motivation during some operational/physical tasks. Finally some of the criteria used in selecting our participants for their job categories were intelligence-based, it seems likely then that our sample was considerably more intelligent than an 'average' population. Randall, Shneerson, & File (2005) found the beneficial effects of

modafinil to be moderated by IQ. That is, more intelligent individuals showed less performance improvement under modafinil. Thus it is possible our participants received less benefit from modafinil than participants in some previous studies.

One intriguing finding of this study was the significant, but mild, effect of modafinil on sleep. Our study noted more sleep movement and less sleep duration, under the modafinil condition, during the one 2-hr nap allowed in the study (Figure 3). It did not greatly impair sleep as is commonly seen with use of amphetamines; but, did create a more restless sleep (as indicated by wrist actigraph counts) than those taking placebo. In the one study, with a similar population, relating to this issue, Saletu, Frey, Krupka, Anderer, Grünberger, and Barbanoj (1989) found several significant sleep disturbance effects attributable to modafinil (200mg dose) in a single night of sleep following dosing.

The post study survey of the participants documented repeated praise for the improved cognitive functioning attributed to the medication. These comments noted that modafinil "keeps you mentally focused when it is hard to stay focused," and "improved mental alertness of operators engaged in surge operations." Generally, expressed advantages include: 1) enhanced mental acuity and alertness, 2) wakefulness when needed, and 3) reduced sleep drive with minimal impact on sleep ability. The primary disadvantage they noted was a sentiment that the dose was not strong enough as the effect wore off too soon. The participants indicated an interest in taking higher doses in order to get a stronger or a more prolonged effect. Eleven of the twelve participants accurately guessed when modafinil was given, clearly revealing a participant awareness of medication use as opposed to placebo use. The fact that they could correctly discriminate drug from placebo dosing lends credence to the above remarks in spite of minimal identifiable improvement in some of the cognitive tests used in this study. Finally, 100% of participants stated modafinil would be operationally useful.

As has been seen in previous studies, side effects from modafinil are minimal for this dosing scheme. Headache and nausea were the only symptoms more pronounced under modafinil. These symptoms were generally reported as 'slight', although two participants reported 'severe' nausea. This finding indicates that there may be a population of people who are relatively sensitive to modafinil; however, the sample size of this study is too low to test such a hypothesis.

CONCLUSIONS

The results of this study provide some evidence that modafinil partially attenuates the performance decrement caused by sleep loss in field environments, thus increasing the likelihood of successful mission accomplishment. As anticipated, modafinil had very little impact upon physical performance, had no adverse physiologic effects, and produced few side effects. Modafinil may negatively impact sleep but the effect appears minimal and should be investigated in a controlled manner. The universal acceptance of modafinil by our participants, its observed mild performance advantages, and its low health risk, make it a candidate for field applications.

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Appendix A. Descriptive Statistics (Means and Standard Deviations) and Statistical Test Results for Objective and Subjective Field Tests

			Data Collection Times				ANOVA Results			
Test	Variable	Drug	Day1	Day2	Day3	Day4		Drug	Time	Drug X Time
Live Fire	Score	Modafinil	28.3 7.6	29.3 6.0	29.8 5.1	28.8 7.2	MSE df F p	33.47 (1,11) 1.53 .243	14.80 (3,33) 1.27 .300	20.53 (3,33) .136 .938
		Placebo	28.9 6.7	31.6 4.3	31.2 6.5	30.3 6.7				
Obstacle Course	Total Time	Modafinil		385.9 47.3	362.3 66.2		MSE df F p	3781.36 (1,6) .317 .594	3200.64 (1,6) 1.31 .296	2873.19 (1,6) .002 .967
		Placebo		399.8 83.6	374.5 59.7					
Physical Exertion	Score	Modafinil	12.2 1.9	14.0 1.5	14.0 1.8		MSE df F p	7.81 (1,10) .012 .915	4.51 (1,12)[h] 11.03 **.005**	.92 (2,20) .276 .762
		Placebo	11.9 2.3	14.1 2.4	14.1 2.4					
Mental Exertion	Score	Modafinil	3.00 .78	3.27 .79	3.36 .51		MSE df F p	0.436 (1,10) .312 .588	0.454 (2,20) 1.73 .202	0.200 (2,20) .000 1.000
		Placebo	2.91 .83	3.18 .60	3.27 .47					
Fitness Test	3.0 mile run(sec)	Modafinil	1321 89	1298 105	1340 112		MSE df F p	3558.60 (1,6) .906 .378	6193.40 (1,8)[h] .330 .637	2045.75 (2,12) 1.41 .283
		Placebo	1324 97	1349 153	1339 149					
	Pull ups	Modafinil	16.0 3.8	14.6 2.4	14.0 4.0		MSE df F p	5.045 (1,10) .108 .749	10.858 (1,15)[h] 6.64 **.014**	9.566 (1,13)[h] 1.38 .272
		Placebo	17.5 5.8	13.6 2.5	14.1 2.7					
	Push ups	Modafinil	85.7 1.4	84.8 1.6	84.8 4.2		MSE df F p	14.434 (1,11) 1.86 .200	11.510 (2,22) .150 .862	5.556 (2,22) .280 .758
		Placebo	86.3 4.1	86.2 2.3	86.4 6.7					
	Sit ups	Modafinil	110.3 19.8	108.2 14.6	104.5 18.7		MSE df F p	9.479 (1,10) .040 .846	179.849 (1,12)[h] .511 .521	201.070 (2,20) 1.077 .360
		Placebo	107.6 13.9	103.5 8.9	111.5 24.1					
	Swim (sec)	Modafinil	1570 118	1536 146	1564 166		MSE df F p	8644.7 (1,9) .515 .491	4781.5 (2,18) .724 .499	1924.3 (2,18) .664 .527
		Placebo	1536 183	1531 171	1552 181					
Scenario Efficiency	Score	Modafinil	47.8 11.9	46.4 6.7	48.8 6.7		MSE df F p	42.783 (1,4) 2.03 .228	126.633 (2,8) .155 .859	55.033 (2,8) .013 .987
		Placebo	44.0 10.2	42.8 10.1	46.0 10.9					
Radio Evaluation	Errors	Modafinil			.50 .84	.17 .41	MSE df F p	0.742 (1,5) .056 .822	0.142 (1,5) 7.35 **.042**	0.742 (1,5) .056 .822
		Placebo			.67 1.03	.17 .41				
	Response Time	Modafinil			317.8 123.0	235.3 63.9	MSE df F p	15262 (1,5) .521 .503	2469 (1,5) 7.60 **.040**	4102 (1,5) 1.03 .356
		Placebo			254.8 86.9	225.5 87.0				

Notes: 1. Numbers in each cell of the table represent the mean (top) and standard deviation (bottom).
2. [h] Huynh-Feldt adjustment was made to the anova degrees of freedom.

Appendix B: Descriptive Statistics (Means and Standard Deviations) and t-test Results for Subjective and Objective Nap Measures

Source	Variable	Drug	Mean (Std Dev)	t-test Results	
				t (df)	P (1-tailed)
Actigraph Data	Mean Activity (min)	modafinil	6.9 (5.7)	2.09 (8)	.035
		placebo	3.1 (1.8)		
	Sleep Minutes	modafinil	103.6 (10.9)	-2.00 (8)	.040
		placebo	110.6 (7.7)		
Subjective Survey	Sleep Length	modafinil	103.8 (11.9)	-1.8 (11)	.048
		placebo	110.0 (13.3)		
	Sleep Score	modafinil	3.6 (.7)	-1.6 (11)	.070
		placebo	4.1 (.8)		

Appendix C. Descriptive Statistics (Means and Standard Deviations) and Statistical Test Results for Cognitive, Subjective, and Physiologic Variables

			Data Collection Time Points						ANOVA Results			
Test	Variable	Drug Condition	Day 1 1600hr	Day 2 0400hr	Day 2 1600hr	Day 3 0400hr	Day 3 1600hr	Day 4 0400hr		Drug	Time	Drug x Time
Math Processing	Accuracy (%)	Modafinil	95.2 5.0	92.9* 6.7	90.8 8.2	90.4* 12.5	93.2 6.3	86.0 12.9	MSE df	83.506 (1,11)	99.66 (2,25)[h]	89.82 (4,42)[h]
		Placebo	94.9 5.7	88.6* 7.7	89.9 9.8	78.5* 17.1	92.6 6.4	84.3 16.3	F p	4.61 **.055**	9.44 **.001**	1.76 .159
	Lapses (count)	Modafinil	.50 .80	1.08 1.08	2.00 2.34	1.75 2.49	.67 .89	2.50 2.68	MSE df	7.020 (1,11)	4.078 (3,32)[h]	5.309 (4,41)[h]
		Placebo	.42 .67	1.50 1.45	1.67 2.31	4.67 3.85	1.17 1.80	2.75 3.47	F p	1.92 .194	10.93 **<.001**	2.09 .104
	MRTC (msec)	Modafinil	2143 529	2258 418	2348 476	2354 508	2234 476	2400 501	MSE df	148544 (1,11)	50802 (5,55)	80252 (3,36)[h]
		Placebo	2150 506	2401 471	2305 486	2579 501	2175 428	2454 585	F p	.716 .415	7.21 **<.001**	1.42 .253
	SDRTC (msec)	Modafinil	753 174	753 149	800 142	800 214	767 128	852 215	MSE df	15477 (1,11)	12064 (5,55)	32317 (3,32)[h]
		Placebo	722 178	793 106	801 191	921 183	752 168	871 146	F p	1.22 .294	5.45 **<.001**	.944 .429
	Thruput (# correct resp/min)	Modafinil	28.2 7.1	25.4 5.6	24.3 6.6	23.9 5.8	26.1 6.2	22.5 8.2	MSE df	19.372 (1,11)	9.469 (5,55)	21.364 (3,30)[h]
		Placebo	27.7 7.0	23.0 5.7	24.5 6.8	19.1 6.2	26.6 6.8	22.3 7.9	F p	2.62 .134	14.62 **<.001**	2.07 .129
PVT	Lapses (count)	Modafinil	1.3 1.4	8.1 12.7	11.1 15.4	18.3 14.2	12.0 14.4	22.4 9.4	MSE df	100.38 (1,6)	77.77 (5,30)	65.62 (5,30)
		Placebo	3.6 4.3	8.0 7.4	9.1 9.2	21.1 12.5	5.3 2.4	16.7 11.0	F p	.517 .499	8.52 **<.001**	.857 .521
	MRRT (1/sec)	Modafinil	4.4 .5	3.7 1.0	3.4 1.1	2.8 1.0	3.5 .8	2.3 1.0	MSE df	.748 (1,6)	.454 (4,26)[h]	.299 (5,30)
		Placebo	4.1 .4	3.6 .7	3.5 .5	2.4 .8	3.6 .3	2.8 .7	F p	.001 .973	15.01 **<.001**	1.265 .305
	MRT (msec)	Modafinil	243 34	498 563	804 1188	1190 1317	512 378	1543 1481	MSE df	588377 (1,6)	1718764 (3,19)[h]	514444 (2,12)[h]
		Placebo	271 48	404 200	471 236	1514 1553	331 47	944 1217	F p	.724 .427	2.78 **.069**	1.64 .233
	SDRRT (1/sec)	Modafinil	.78 .17	.88 .27	.89 .28	1.15 .24	1.02 .34	1.20 .15	MSE df	.044 (1,6)	.048 (5,30)	.09 (3,17)[h]
		Placebo	.91 .26	1.11 .22	1.15 .39	1.19 .11	.95 .18	1.11 .25	F p	3.33 .118	4.29 **.005**	1.45 .264
	SDRT (msec)	Modafinil	83 56	481 891	1002 1941	1901 2332	716 796	2006 1868	MSE df	1801137 (1,6)	3908327 (3,18)[h]	525821 (5,30)
		Placebo	119 81	395 408	834 967	2320 2133	253 198	1112 1669	F p	.433 .535	3.52 **.037**	1.33 .277

Grammatical Reasoning	Accuracy (%)	Modafinil	91.2 13.1	89.8 7.98	84.1 19.0	74.1 20.8	91.6 8.4	83.0 16.5	MSE df	629.97 (1,10)	161.22 (4,41)[h]	161.22 (4,41)[h]
		Placebo	92.5 4.3	86.6 12.5	90.6 8.5	74.5 17.9	92.4 5.7	76.0 24.9	F p	.001 .973	4.56 **.004**	.458 .772
	Percent Lapses (%)	Modafinil	.00 .00	.88 2.15	5.47 8.97	6.29 9.84	.93 2.27	7.49 8.25	MSE df	58.620 (1,10)	30.457 (5,50)	30.457 (5,50)
		Placebo	.83 2.04	2.63 6.45	.00 .00	6.42 6.58	1.67 4.08	5.88 7.81	F p	.111 .745	2.82 **.026**	.683 .638
	MRTC (msec)	Modafinil	5670 1746	6429 1346	6279 1530	6264 1119	5490 1398	7433 1820	MSE df	9928030 (1,10)	931525 (5,50)	931525 (5,50)
		Placebo	5781 981	6020 1377	5499 1483	6377 2549	5889 1183	6890 1579	F p	.062 .808	3.91 **.005**	.676 .643
	SDRTC (msec)	Modafinil	1436 566	2009 735	2364 1204	2767 1093	1811 939	2497 883	MSE df	2048946 (1,10)	372650 (5,50)	372650 (5,50)
		Placebo	1675 607	1892 588	1762 719	2335 777	1748 326	2398 846	F p	.281 .608	4.74 **.001**	.710 .619
	Thruput (# correct resp/min)	Modafinil	10.3 3.5	8.7 2.3	8.8 3.5	7.0 2.4	10.4 3.0	7.1 3.0	MSE df	40.516 (1,10)	3.617 (4,39)[h]	3.617 (4,39)[h]
		Placebo	9.9 1.6	9.1 3.5	10.6 3.3	7.9 3.8	9.7 2.1	7.1 3.3	F p	.055 .819	7.43 **<.001**	.962 .438
Profile of Mood States	Anger (std score)	Modafinil	40.7 8.0	44.0 10.2	41.0 8.1	41.0 6.0	42.3 7.1	41.1 6.8	MSE df	43.67 (1,11)	41.75 (2,24)[h]	49.27 (2,27)[h]
		Placebo	40.7 5.1	41.2 5.3	40.9 5.2	43.4 8.4	40.9 5.3	41.3 4.9	F p	.064 .806	.752 .491	.738 .514
	Confusion (std score)	Modafinil	36.2 2.0	40.2 6.2	38.9 7.6	39.3 4.8	38.7 2.5	39.2 6.5	MSE df	32.00 (1,11)	8.62 (5,55)	15.33 (3,33)[h]
		Placebo	36.3 2.7	39.3 3.2	40.3 3.1	41.6 4.0	39.3 3.2	40.8 3.2	F p	.834 .381	6.21 **<.001**	.881 .460
	Depression (std score)	Modafinil	37.8 2.0	41.3 8.5	39.2 6.9	39.9 7.7	39.3 4.6	39.3 7.2	MSE df	20.30 (1,11)	19.19 (2,24)[h]	9.51 (3,35)[h]
		Placebo	38.4 2.5	39.0 3.9	39.0 4.0	39.8 4.1	39.4 3.9	39.9 4.5	F p	.067 .800	1.41 .264	1.11 .360
	Fatigue (std score)	Modafinil	37.2 4.1	45.7 9.4	44.7 9.4	44.4 6.5	46.9 5.1	47.2 7.0	MSE df	170.51 (1,11)	26.64 (5,55)	22.51 (5,55)
		Placebo	38.3 6.4	46.3 8.2	46.4 7.9	49.0 7.0	46.3 5.8	47.3 7.3	F p	.323 .581	11.70 **<.001**	.904 .485
	Tension (std score)	Modafinil	35.8 2.3	37.9 6.1	37.0 4.9	38.0 5.1	38.1 4.8	37.8 6.0	MSE df	11.96 (1,11)	10.65 (3,28)[h]	3.96 (5,55)
		Placebo	35.9 2.0	37.2 3.7	37.5 3.7	38.2 3.3	37.3 3.3	37.9 3.2	F p	.037 .851	2.83 **.063**	.453 .810
	Vigor (std score)	Modafinil	36.0 12.5	33.1 9.1	33.5 8.4	31.3* 5.3	32.8* 5.8	31.5 7.3	MSE df	35.70 (1,11)	85.15 (2,19)[h]	35.27 (3,29)[h]
		Placebo	34.8 7.9	30.5 5.6	29.3 4.1	28.3* 3.6	30.0* 4.5	29.0 3.9	F p	7.47 **.019**	3.23 **.069**	.281 .817
Sleep Scale	Sleepiness Score	Modafinil	2.5 .8	4.2 1.6	3.8 1.1	4.7 1.3	3.8 1.6	4.3 1.3	MSE df	3.674 (1,11)	1.279 (5,55)	.508 (5,55)
		Placebo	2.6 .5	4.3 1.6	4.6 1.2	5.2 1.7	4.2 1.6	5.0 1.6	F p	1.70 .219	12.98 **<.001**	.952 .455

Physiologic (Vitals)	Heart Rate	Modafinil	72.5 13.5	65.4 8.0	67.6 11.6	63.2 7.9	63.5 9.8	61.1 11.8	MSE df	71.13 (1,11)	72.74 (5,55)	66.95 (4,46)[h] .990
		Placebo	68.4 8.4	65.8 11.0	65.1 8.8	57.4 8.7	66.1 16.6	57.9 9.1	F p	2.23 .163	5.47 **<.001**	.425
	Systolic BP	Modafinil	125.1 10.1	124.1 7.5	129.8 9.14	129.7 9.4	132.5 13.2	126.9 9.8	MSE df	125.23 (1,11)	63.70 (5,55)	64.72 (5,55)
		Placebo	127.8 12.7	129.5 7.0	125.4 8.2	129.4 10.7	128.8 8.3	130.8 7.9	F p	.112 .744	1.03 .412	1.51 .201
	Diastolic BP	Modafinil	71.8 11.5	69.3 10.0	69.3 9.1	72.9 8.9	71.6 8.4	70.4 4.8	MSE df	88.77 (1,11)	60.69 (5,55)	55.12 (5,55)
		Placebo	70.8 6.7	70.8 7.9	71.1 6.5	70.5 9.6	69.6 7.1	67.2 9.2	F p	.310 .589	.417 .835	.485 .786
	Temperature	Modafinil	98.08 .72	97.66 .60	98.10 .54	97.21 .38	97.73 .78	97.24 .51	MSE df	1.260 (1,11)	3.931 (1,16)[h]	5.542 (1,15)[h] .746
		Placebo	98.21 .73	97.46 .54	97.83 .59	97.13 .61	96.59 3.73	96.87 .61	F p	2.94 .114	4.56 **.038**	.443
Jump Test	Average Height	Modafinil	No Data Available		.28 .05	.26 .05	.27 .07	.22 .04	MSE df	.000584 (1,6)	.000503 (3,18)	.000636 (3,18)
		Placebo			.26 .05	.24 .07	.26 .05	.20 .06	F p	7.78 **.032**	18.20 **<.001**	.244 .865
	Average Power	Modafinil	No Data Available		6956 9143	3470 1062	3725 1418	3518 1924	MSE df	8814826 (1,6)	27548568 (1,6)[h]	24603416.13733 (1,8)[h]
		Placebo			3487 1145	3839 2876	3704 1233	2925 1287	F p	1.37 .286	1.09 .342	1.03 .363
	Average Work	Modafinil	No Data Available		331 66	326 66	328 79	291 57	MSE df	2212.7 (1,6)	462.74 (3,18)	334.28 (3,18)
		Placebo			323 66	302 73	320 65	268 76	F p	1.61 .252	14.16 **<.001**	.735 .545

Notes: 1. Numbers in each cell of the table represent the mean (top) and standard deviation (bottom).
3. [h] Huynh-Feldt adjustment was made to the anova degrees of freedom.
4. * indicates significant differentce between modafinil and placebo.