NAVAL MEDICAL RESEARCH UNIT DAYTON

The Effects of Modafinil and OTC Stimulants on Physical and Cognitive Performance

J. Lynn Caldwell, Beth M. Hartzler, Chelsea B. Levin, Christina L. Kunkle, Miya Y. Hayes, Svyatoslav Y. Guznov, Wilfred H. Wells, William J. Becker, Richard V. Folga, and Michael Tapia

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J. M. Andrews

Jeffrey M. Andrews, CAPT, MSC, USN
Commanding Officer

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The study protocol was approved by the Naval Medical Research Unit Dayton Institutional Review Board in compliance with all applicable Federal regulations governing the protection of human subjects.

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SUMMARY

Performance effects due to insufficient sleep have been documented for decades. Given the prevalence of caffeine as a fatigue countermeasure among military personnel, and the availability of modafinil to select populations, commanders and medical staff have expressed concern over the safety of potentially combining the two alertness aids. The present study compared the combined effects of modafinil and caffeine with those of either substance alone during 37 h of continuous wakefulness. Participants were randomly assigned to one of four groups: modafinil (200mg), caffeine (200mg), modafinil-caffeine (200mg each), or placebo. Following training and baseline, participants received their respective treatment at 2300 (18 h awake). At midnight, participants walked 2 miles on the treadmill with a 30-lb back pack at 3 miles per hour. Cognitive performance, subjective mood, and vital signs were measured every 3 h starting at 0200 for a total of 5 test sessions. The results indicated that modafinil, whether alone or in combination with caffeine, increased alertness and performance across the 37-hour period of continuous wakefulness. When combined with caffeine, the effects were the same for most of the cognitive measures. The subjective side effects and vital signs did not increase with the combination of the two alertness aids, including those vital signs taken while walking on the treadmill. In this select group of study participants, the combination of caffeine with modafinil does not appear to improve or inhibit performance above that with modafinil alone.

1.0 INTRODUCTION

Fatigue among military service men and women, and the general American workforce, has long been a concern of researchers and government agencies, and estimates have suggested that the effects of sleepiness on work productivity cost Americans as much as $54 million per year (Rosekind et al., 2010). Research has found that employees working shifts longer than 12 hours often exhibit a decrease in job performance and efficiency (Caruso, 2014). The ability to quickly and effectively execute different tasks and actions may be critical to a successful mission, but long periods of inactivity during a mission may reduce the aircrew's preparedness for any mission-critical activity (Gore, Webb, & Hermes, 2010). Thus, while engaged in a sustained operation, safety and success of a mission may depend upon the soldier's ability to stay alert and focused on the task at hand, but for many getting the sleep necessary to remain vigilant is not possible.

In response to the need for attentiveness despite fatigue, guidelines and resources have been developed which are intended to ensure that the execution of a mission will not suffer. For example, in addition to regulations regarding sleep schedules and exercise during Operations Desert Shield and Desert Storm, an important part of the "Aircrew Conditioning Program" was the administration of dextroamphetamine to flight crews preparing for critical missions (Emonson & Vanderbeek, 1995). More recently, Gore and colleagues (2010) explained that the United States Air Force has worked to improve fatigue countermeasures, such as developing duty hour limitations, improving sleeping conditions to control sound and light, and offering hypnotics to induce sleep when time permits. Despite these formal efforts to reduce fatigue among military personnel, recent surveys have found that, in addition to using prescription alertness-enhancing medications such as modafinil, deployed military personnel are also using over-the-counter stimulants (Lieberman et al., 2010). This finding has raised concerns among the medical community over the safety and efficacy of combining prescribed and over-the-counter stimulants.

Stimulants have long been used by members of the military in order to maintain alertness and high levels of performance (Babkoff & Krueger, 1992). In recent years, modafinil has become a means of alleviating the symptoms of fatigue among military personnel when scheduling and other behavioral countermeasures have been ineffective (Baranski, Pigeau, Dinich, & Jacobs, 2004). The tendency of some personnel to prefer modafinil to dextroamphetamine may be due to the side effects associated with dextroamphetamine use such as difficulty in obtaining recovery sleep (Baranski, Cian, Esquivié, Pigeau, & Raphel, 1998) and concerns over the effect on the cardiovascular system (Caldwell, 2001). In addition, studies have found that modafinil is less addictive and has fewer side effects than dextroamphetamine (Baranski et al., 2004). Research has indicated that administering modafinil to treat fatigue associated with inadequate sleep can lead to significant improvement over placebo on measures like the Psychomotor Vigilance Task (PVT; Wesensten, Killgore, & Balkin, 2005) as well as tests of reaction time, mental addition, and short-term memory (Baranski et al., 1998). When modafinil was administered to night-shift workers who had been diagnosed with shift-work sleep disorder, the results indicated that response time and number of lapses on the PVT decreased from baseline performance, and these workers reported fewer accidents and near-accidents during the drive home after work (Czeisler et al., 2005). In a laboratory study, Killgore et al. (2008) determined that sleep-deprived

participants who were given modafinil demonstrated less risk-taking behavior in comparison to their baseline measurements on the Evaluation of Risk Scale (EVAR) and the Balloon Analogue Risk Task than those taking a placebo. Baranski and colleagues (2004) reported similar benefits when modafinil was given to non-sleep deprived participants. Compared to placebo, participants taking modafinil showed a decrease in fatigue with concurrent improvements in motivation, reaction time, and vigilance in a variety of cognitive tasks.

In addition to prescribed countermeasures, there are many over-the-counter means of alleviating fatigue. Among the most popular of these is caffeine, which is widely available in substances from coffee, soda, and energy drinks to capsules and chewing gum (Lieberman et al., 2012). In comparison to placebo treatment, research has found that giving sleepy participants caffeinated coffee led to a reduction in the number of major and minor incidents on a simulated driving task (Horne & Reyner, 1996; Philip et al., 2006). When caffeine was administered in pill form to both well-rested and sleep-deprived participants, Lorist and colleagues (1994) found that response times for both groups were significantly lower than for participants who took the placebo, and that the participants who received caffeine also had a lower number of errors of omission and commission on a stimulus degradation task. Additional research determined that participants who were given 600mg of caffeine after 64 hours of continuous wakefulness demonstrated superior reaction times on the Psychomotor Vigilance Task, as well as less cognitive impairment as assessed by the Bieber Cognitive Estimation Task (Wesensten, Killgore, & Balkin, 2005). Killgore et al. (2008) evaluated the effect of administering caffeine to participants who had been awake for 44 hours. In comparison to baseline measures, these participants demonstrated significantly lower levels of risk-taking behavior on several subscales from the Evaluation of Risks Scale (e.g., Energy, Self Control, and Total Risk-Taking).

In addition to reports on the effect of stimulants on cognitive performance, there has been research to determine whether substances such as modafinil and caffeine can improve physical performance. The effects of modafinil appear to differ when performance is assessed during sleep deprivation than when assessed where sleepiness is not a factor. For example, Jacobs and Bell (2004) determined that 4mg/kg with no sleep deprivation was sufficient to improve participants' performance on a stationary bicycle. After administration of either a placebo or modafinil to well-rested participants, those who ingested modafinil demonstrated a significant increase in the amount of time to exhaustion as well as an increase in maximal aerobic power and heart rate in comparison to the performance of participants who ingested the placebo. In a study where sleep deprivation was a factor, Cuddy, Reinert, Hansen, and Ruby (2008) determined that Special Forces operators evaluated during 72 hours of continuous wakefulness showed no difference in performance between participants given modafinil and those given a placebo on tasks such as a three-mile run and a one-mile swim. Further, the maximum number of pull-ups, as well as a measurement of the participant's total energy expenditure during the study did not differ significantly between the modafinil and placebo groups.

Research examining the effects of administering caffeine has also indicated that this over-the-counter stimulant may benefit soldiers on tasks assessing endurance and vigilance. Testing the effect of administering caffeine or placebo treatment in 2 doses (second dose at half the strength and 6 hours after the initial dose), Gillingham, Keefe, and Tikuisis (2004) found that among trained marksmen tested after fatiguing exercise, participants who were given caffeine for both

doses performed better at detecting threatening targets and time to engagement during the vigilance task than did participants who were given a placebo for one or both doses. Likewise, McLellan and colleagues (2005) tested the performance of Special Forces personnel on running speed, marksmanship, and vigilance throughout a 27-hour continuous wakefulness period, giving the soldiers either caffeinated gum or a placebo gum. Although the caffeine gum did not appear to improve marksmanship of soldiers over that of those who received the placebo gum, vigilance was significantly superior. These participants also improved on their running speed from the baseline measure, whereas the soldiers who received the placebo gum had slower running speeds in comparison to the baseline measure.

The present study was developed to address questions and concerns expressed by the Air Force Special Operations Command (AFSOC) commanders and medical staff who have observed the high intake of caffeine-containing energy drinks by AFSOC personnel. The question arose about the safety and performance effects, either beneficial or harmful, which may occur if over the counter (OTC) stimulants are consumed in addition to the "go-pills" which are prescribed during certain missions. Therefore, this study investigated both cognitive and physical measures of personnel through 37 hours of continuous wakefulness during which both modafinil and caffeine were consumed. Since caffeine is the active ingredient in the OTC substances which affect cognitive performance, the present study chose this stimulant to represent the popular OTC substances consumed by AFSOC personnel. The study protocol was approved by the Naval Medical Research Unit Dayton Institutional Review Board in compliance with all applicable Federal regulations governing the protection of human subjects. The sponsor for this study was the Air Force Medical Support Agency Office of Medical Modernization (AFMSA/SG9). Funds were distributed by the Defense Health Program (DHP).

Hypotheses tested:

1) Participants' cognitive and physical performance would be different following consumption of an intervention (either caffeine or modafinil) compared to placebo.
2) Participants' performance would be different following consumption of both caffeine and modafinil (consumed together) compared to performance following placebo.
3) Participants' performance would be different following consumption of both caffeine and modafinil (consumed together) compared to performance following consumption of either substance alone.

Other objective(s)

1) Determine whether combining caffeine and modafinil would increase side effects compared to either substance alone.
2) Determine whether sleep architecture would differ following consumption of both substances (consumed together) compared to either alone or to placebo.
3) Assess whether an individual's stress profile correlated with performance following sleep deprivation.
4) Determine whether sleep deprivation affected depth perception.
5) Examine the feasibility of identifying fatigue with breath biomarkers.

2.0 METHOD AND PROCEDURES

2.1 Prestudy questionnaires and assessments

This laboratory-based study was a mixed-model design in which 4 groups of participants were exposed to 3 days of testing with no sleep for a 40-hour period. During this period, participants received either a placebo treatment, modafinil (200mg), caffeine gum (200mg), or a combination of modafinil and caffeine, depending on the group to which he was assigned.

2.1.1 Questionnaires. The following is a list of assessments taken prior to baseline day. Personality and circadian type questionnaires were administered prior to data collection in order to determine whether any of the participants were extreme morning or evening types, and to quantify certain personality factors (e.g., neuroticism, extraversion). Results from the personality questionnaires were used for potential covariates. Sleep/wake data were collected to assure participants attained adequate sleep each of the 3 days prior to their training day. Vision testing was administered to record various visual characteristics which may influence some of the vision tests.

2.1.1.1 The *Horne and Östberg Morningness/Eveningness Questionnaire* (Horne & Östberg, 1976) was used to subjectively evaluate each participant's circadian type and was administered when participants arrived at the laboratory for the beginning of the study. This 19-item questionnaire was presented on a computer screen and scored automatically by the program.

2.1.1.2 The *Revised NEO Personality Inventory (NEO-PI-R)* is a widely used instrument for the assessment of personality functioning (Costa & McCrae, 1992). The inventory consists of 240 items answered on a 5-point scale, ranging from "strongly disagree" to "strongly agree". The five domains measured are: Neuroticism, Extraversion, Openness to experience, Agreeableness, and Conscientiousness. Each domain is further subdivided into six facets that measure specific features of the primary personality factor. The inventory was completed when participants arrived at the laboratory for the beginning of the study.

2.1.2 Activity/sleep monitor. The Motionlogger Micro Sleep Watch® (actimeter), from Ambulatory Monitory, Inc., is a water-resistant, wrist-worn device that measures frequency and intensity of wearer movement using a precision motion sensitive piezoelectric assembly. A 1-minute data capture epoch length was used to collect movement data. The movement results were plotted using accompanying software to track subject sleep patterns. Participants were given the actimeter on Friday prior to the in-house portion of the study and instructed to wear the watch for the next 3 days. The data were reviewed for compliance with the sleep requirement on Monday afternoon, the first day of the in-house portion of the study. Study volunteers who did not sleep at least 7 hours per night were either rescheduled until the sleep requirements were met or dropped from the study.

2.1.3 Vision testing. Vision screening was performed following the cognitive sessions on the training day. All participants were screened individually using a variety of vision measurements. Screening began with the Armed Forces Vision Tester (Stereo Optical OPTEC 2300), which

measured near and far vertical phoria, near and far lateral phoria, and far depth perception. Participants responded verbally while an experimenter recorded the results. Visual acuity, stereo acuity, and vergence were then measured at a computer workstation with the room lights dimmed. Participants responded using a handheld controller and the computerized assessments were scored automatically. Visual and stereo acuity were measured at a distance of 5 meters. Visual acuity was measured using the Landolt C stimulus test, first measuring each eye separately and then both eyes together. Stereo acuity was measured using the Bars in Depth Stereo Acuity Test while the participants wore shutter glasses. Vergence was measured at a distance of 32 inches, again while the participants wore shutter glasses. Participants were instructed to be as accurate as possible for all screening tests and responses were not timed.

2.2 Performance tests and questionnaires

The following is a list of cognitive and physical tasks, questionnaires, and physiological assessments included in the study to evaluate the effects of fatigue and treatment on performance, mood, and physical state. The total amount of time required to complete the testing session was approximately 2 hours.

2.2.1 Mood and side effects assessments. Mood was measured with two questionnaires, the Profile of Mood States (POMS) and Visual Analogue Scale (VAS), and participants indicated any side effects they may have experienced on the Side Effects questionnaire. These assessments were administered at the end of each of the testing sessions.

2.2.1.1 The *POMS* (McNair, Lorr, & Droppleman, 1981) is a paper-and-pencil questionnaire consisting of 65 items which measure affect on 6 scales: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. A Total Mood Disturbance score is calculated based on all the items in the questionnaire. The questionnaire was administered and scored by computer.

2.2.1.2 The *VAS* consists of eight 100 mm lines centered over the adjectives ‘alert/able to concentrate’, ‘anxious’, ‘energetic’, ‘feel confident’, ‘irritable’, ‘jittery/nervous’, ‘sleepy’, and ‘talkative’ (Penetar et al., 1993). At the extremes of each line, ‘not at all’ and ‘extremely’ were printed respectively. Scores consist of the distance of the participant’s mark from the left end of the line (in mm). This questionnaire was presented on a computer screen and scored by computer program.

2.2.1.3 Side-effects were assessed via a questionnaire. Participants were shown a list of possible symptoms which included those associated with stimulant use (e.g., headache, tremor, anxiety, etc.) and asked to indicate whether and to what degree they were currently experiencing that side effect. Responses were made on a 5-point scale, ranging from “not at all” to “extremely”.

2.2.2 Cognitive tests. A series of cognitive evaluations were measured during the training, baseline, and continuous wakefulness period. Tests measured participants’ ability to maintain attention, reaction time, inhibition control, risk taking tendency, and tracking performance.

2.2.2.1 Flight simulator performance. Flight simulator performance was measured using the X-Plane® 9 flight simulator (Laminar Research, Columbia, SC). Participants were given a simple flight profile, with instructions to fly "straight and level" at an altitude of 2000 feet, airspeed of 140 knots, and a heading of 180 degrees (south), for 25 minutes. The first 5 minutes of the "flight" allowed the participant to obtain steady flight, with the final 20 minutes scored for accuracy. Root mean square error (RMSE) was calculated for all parameters. Figure 1 illustrates the view seen by the participants for this test.

Figure 1. Screen display for the flight simulator.

2.2.2.2 Psychomotor Vigilance Test (PVT). Reaction time was assessed using the 10-minute PVT, a simple reaction time test known to be sensitive to sleep loss (Dinges et al., 1997). The PVT requires sustained attention and discrete motor responses. The 8" x 4.5" x 2.4" portable, battery-operated device visually displays numbers counted up by milliseconds in a window. The stimulus is presented for up to 1 minute (60,000 msec), allowing the participant to respond. The participant is asked to press a microswitch as quickly as possible once the numbers are displayed and the device records reaction time. The interstimulus interval varies randomly from 2 to 12 seconds. The data were downloaded from the device, stored on a computer, and reduced using custom software for future analysis. Variables selected for statistical analysis include lapses (reaction time greater than 500 ms) and reaction time (RT). Figure 2 shows the PVT device.

Figure 2. The Psychomotor Vigilance Test (PVT).

2.2.2.3 Go/No-Go Task. This task evaluated participants' inhibition control and information processing abilities. In this task, from the Automated Neuropsychological Assessment Metrics (ANAM®) cognitive test battery, the participant was presented with either a capital "X" or

capital “O”. He was required to press the left mouse button as quickly as possible every time he saw the letter “X,” but to ignore presentations of the “O.” The task took approximately 6 minutes to complete. Figure 3 shows the screen when the target letter was shown.

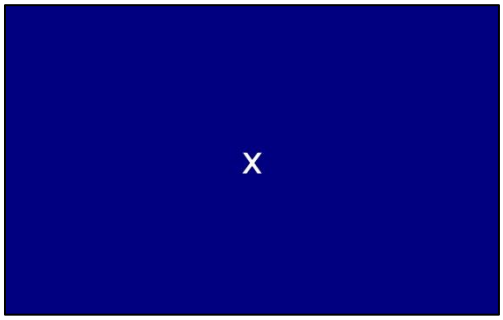

Figure 3. The Go/no-go task.

2.2.2.4 Balloon Analogue Risk Task (BART). The BART is a computer-based task which assesses participants’ risk-taking propensity and has been found to correlate with real world high-risk behaviors (Lejuez et al., 2002) with high test-retest reliability (White, Lejuez, & de Wit, 2008). For the task, participants were shown a deflated balloon and told that for each time they pump up the balloon, they were credited with one point, but warned that after a set number of pumps, the balloon would pop. While pumping the balloon, participants could choose to stop at any time and collect the points they had accumulated in that trial. The number of times that a balloon could be pumped before it popped varied from trial to trial; if it popped, the participant lost all points accumulated on that trial. The maximum number of pumps allowed before an explosion was 128, and the minimum number of pumps before an explosion was 2. The number of pumps before an explosion was randomly-determined by the BART program. The metrics used for analyses included: 1) the number of times the balloon popped; 2) the adjusted average number of pumps (the mean number of pumps for which the balloon did not pop); 3) total score (the total number of points accumulated from unpopped balloons); and 4) cost/benefit ratio (number of exploded balloons / total number of balloons presented (20 in this study). Figure 4 shows the screen view of the BART.

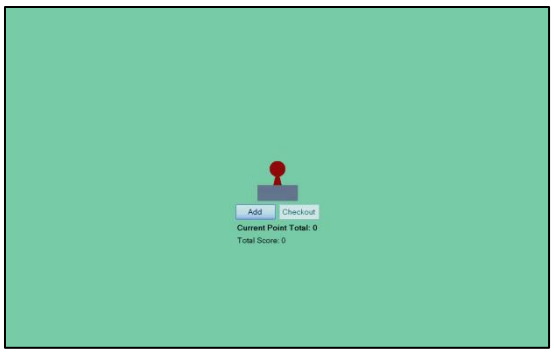

Figure 4. Balloon Analogue Risk Task (BART)

2.2.2.5 Lapse detection. A 2-D visuomotor tracking task, electroencephalogram (EEG) and eye scanning patterns were used to measure lapses in attention. The tracking task was comprised of a target moving continuously with a pseudo-random 2-D pattern on a computer screen. Participants were required to follow a yellow target disc with a computer joystick which moved a red cursor disc. During the task, eye movements were monitored and recorded with a fiber-optic camera. EEG activity was recorded from the electrode sites F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, and O2. The reference electrodes were linked mastoids, with ground placed at site Fpz. Investigators from the New Zealand Brain Institute will analyze these data and publish the results in a separate report. Figure 5 illustrates a tracking pattern from the lapse detection test.

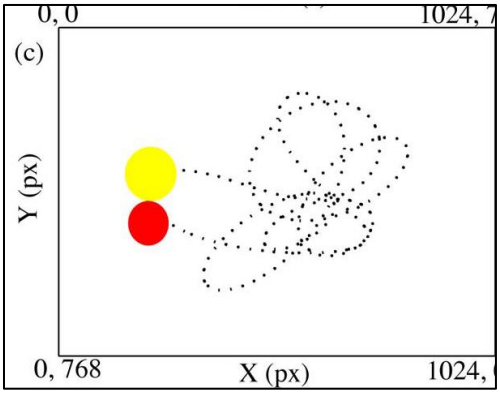

Figure 5. The Lapse detection test.

2.2.3 Physiological assessments. A variety of physiological measures were obtained to determine the effects of the treatment conditions and continuous wakefulness on depth perception, oculometrics, brain activity, and vital signs. A preliminary chemical analysis from breath samples was also planned to identify potential individual differences in response to sleep deprivation.

2.2.3.1 The *Form and Depth Discrimination Test Battery (FDDTB)* consisted of computer-generated test images and observer responses from a game pad. Three tests were included in this battery. In Test 1, the participant was instructed to signal the orientation a Landolt C stimulus (up, down, left, or right) by pushing the corresponding button on the game pad. The test consisted of 40 trials with the accuracy of the observer's response for a range of contrasts used to estimate the participant's Landolt C contrast threshold. Figure 6 shows the Landolt C stimulus.

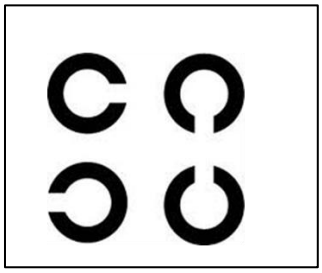
Figure 6. The Landolt C stimulus.

Tests 2 and 3 involved a stereo-acuity test. In Test (2), the participant was required to signal the depth (near or far) of a test bar relative to that of two flanking reference bars. The test had 40 trials and the accuracy of the participant's response for a range of contrasts was used to estimate the participant's depth contrast threshold.

In Test 3, the participant was required to signal the depth (near or far) of a test bar relative to that of two flanking reference bars similar to the stimuli in Test 2. However, in this test, the contrast was fixed at 1.0. Six blocks of 50 trials per block were presented; the speed and accuracy of the participant's response was used to estimate the information accumulation rate. The reference bars were at the same depth as the screen in three blocks; in the remaining three blocks, the reference bars were more distant than the screen. The participants wore shuttered glasses during Tests 2 and 3 which were synchronized to the refresh of the monitor, allowing a measure of stereoscopic depth for Tests 2 and 3. Figure 7 illustrates the stereo-acuity test stimulus.

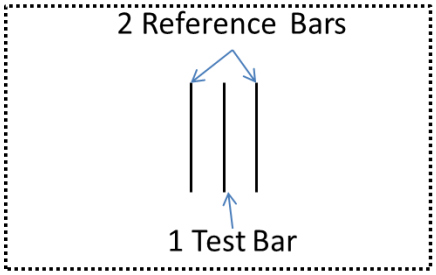

Figure 7. The Stereo-acuity test stimulus.

In addition to the vision tests, a subjective symptom questionnaire was used to assess perceived discomfort during the test. The FDDTB took approximately 20 min to complete. Prior to the baseline test day, participants' baseline vision status (subjective refraction, visual acuity, phoria, vergence, and random-dot stereo-acuity) was assessed to help with the interpretation of the FDDTB. Investigators from the 711th Human Performance Wing will analyze these data and publish the results in a separate report.

2.2.3.2 Oculometrics. The PMI Fitness Impairment Tester (FIT) 2000 (PMI, Inc.) uses eye-tracking and pupillometry to identify impaired physiological states due to fatigue and other factors, such as alcohol or drug use. The system employs an algorithm that compares an individual's present state on four pupillometric variables (saccadic velocity, pupil diameter, pupil constriction amplitude, and pupil constriction latency) to their baseline state data. This task was completed during each session with baseline values being established prior to the continuous wakefulness phase of the study. Each trial required approximately 30 seconds to complete. Figure 8 illustrates the posture of the participant when viewing the stimuli from the FIT.

Figure 8. The PMI FIT device for measuring oculometrics.

2.2.3.3 Electroencephalogram (EEG) recordings. Resting EEGs during eyes closed and eyes open were collected during each session of the study. These data were collected, stored, and analyzed using the Grass Technologies AS40-PLUSamplifier system and TWin® sleep acquisition and review software. Electrode sites included F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, and O2. The reference electrodes were linked mastoids, with ground placed at site Fpz. The sampling rate was set at 400 Hz for each channel, with the time constant at .03 Hz, the low pass filter was set at 35 Hz, and the 60Hz notch filter engaged. Participants were seated in a chair and asked to sit quietly while data were recorded. They focused on a black dot on a white background placed approximately 24 inches directly in front of them. The participant's eyes-open EEG was recorded for 2 minutes, followed by 2 minutes with eyes closed, but awake.

2.2.3.4 Vital signs. Participants' heart rate, temperature, and blood pressure were measured during each session in order to identify any differences which may occur between placebo and treatment conditions.

2.2.3.5 Breath sample for fatigue detection. Breath samples were collected into 5 L Tedlar bags, a standard used by EPA for chemical capture, and in absorbent tubes. For the Tedlar bags, breath samples were exhaled through a disposable syringe connected to the Tedlar bag. A total of 4 to 5 exhalations collected resulted in volume of approximately 2 L. This method of breath collection is compatible with existing THz breath sensor as well as with the equipment used by ALS Environmental. ALS Environmental conducted extensive gas chromatography-mass spectrometry (GC-MS) analysis at the highest level of sensitivity (up to 200 tentative compounds or peaks) attainable with their instrumentation. For the absorbent tubes, breath samples were exhaled into the tube. A total of 2-3 exhalations provided a sufficient breath sample for GC-MS analysis. These data were collected to conduct preliminary analyses on the prospect of finding chemicals which may identify individuals who may be resistant to the effects of sleep deprivation. The results are published in a separate report. Figure 9 shows the bags and absorbent tube for breath sample collections.

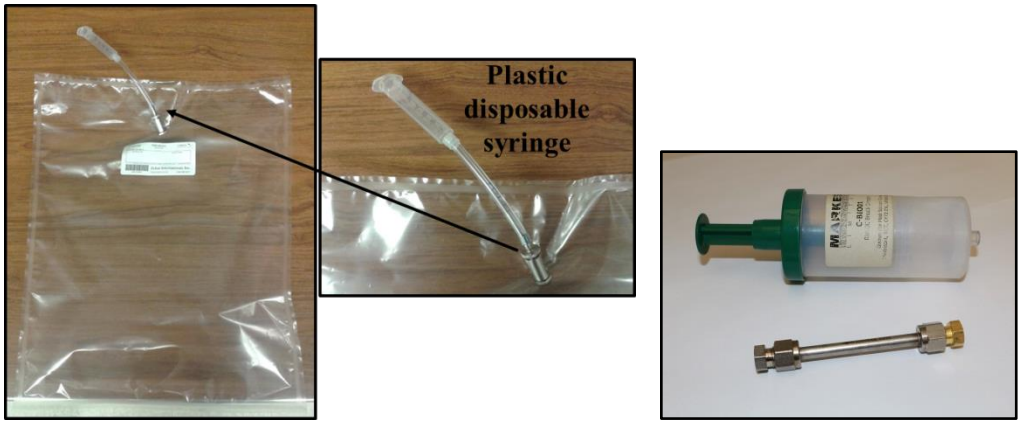

Figure 9. Tedlar bag and absorbent tube.

2.2.4 Polysomnography. Evaluations of sleep architecture during each sleep period were made using an electroencephalograph system. The EEG data from electrodes F3, F4, C3, C4, O1, and O2, referenced to contralateral mastoids (M1 or M2) were recorded. Eye movements (electrooculogram - EOG) were assessed with electrodes affixed slightly above the outer canthus of one eye and slightly below the outer canthus of the other eye and referenced to M1. Muscle activity (electromyogram - EMG) was recorded from submental electrodes (below the jaw) affixed with adhesive collars. The time constant for the EEG channels was 0.3 seconds, and the high filter was 35 Hz. For EOG, the time constant was 5.0 seconds, and the high filter was 10 Hz. For EMG, the time constant was 0.003 seconds, and the high filter was 120 Hz. The 60 Hz notch filter was used. Sampling rate was set at 200 Hz.

2.2.5 Exercise assessments. Participants' resting heart rate and blood pressure were obtained immediately before exercise, both sitting and standing, to establish a resting baseline. Participants performed a 2-mile march on a treadmill while carrying a 30-pound rucksack while heart rate, blood pressure, and subjective physical exertion were collected. The incline of the treadmill was set to 5 degrees and the pace was set at 3 miles per hour. The participants' heart rate and electrocardiograph (ECG) were recorded continuously throughout the treadmill walk. In addition, blood pressure and heart rate were collected from a wrist-worn monitor every 3 minutes while walking on the treadmill to assess the treatments' impact on these vital signs. Following each physiological measurement, participants rated their perceived exertion on a scale of 0 (nothing at all) to 10 (maximal exertion) using the Rating of Perceived Exertion (RPE) Scale. Immediately following the completion of the 2-mile walk, participants' heart rate and blood pressure were measured while sitting, and every 5 minutes for 15 minutes following the walk. The following criteria were used to monitor the vital signs and stop the exercise if limits were exceeded (American College of Sports Medicine, 2010):

1. During exercise, if systolic blood pressure (SBP) appeared to be decreasing with increasing exercise intensity, it was taken again immediately. If a drop in SBP of 10 mmHg or more occurred with an increase in workload, or if it dropped below the value obtained in the standing position prior to testing, the test was stopped, particularly if accompanied by adverse signs or symptoms. Post-exercise blood pressure testing measurements were obtained immediately after exercise, then every 5 minutes until stabilized near baseline level.

2. During the exercise, test heart rate was monitored continuously. After the exercise, test heart rate was obtained every 5 minutes until stable.
3. The test was terminated if the participant reached 85% of age-predicted maximal heart rate (MHR = 206.9-(0.67 x age), failed to conform to the exercise test protocol, experienced adverse signs or symptoms, requested to stop, or experienced an emergency situation.

All treadmill exercises were monitored by an exercise physiologist or by the medical monitor. Participants completed the treadmill walk once each day for the training day, baseline day, and at the beginning of the 40-hour continuous wakefulness period for a total of 3 times. No participant exceeded the limits specified above, although one participant came close to maximum blood pressure limits during the training and baseline days. Since both caffeine and modafinil may increase blood pressure, the medical monitor advised against administering either substance. To avoid completely dismissing the participant from the study, he was given placebo (single-blind).

2.3 Participants

A sample of 40 physically fit individuals was targeted to complete the protocol. Participant characteristics were male, between the ages of 18 and 35, on a day-shift schedule for the past 3 weeks, and active duty military. Qualified participants had a body composition assessment (BCA) at or below 22%. Assessment of body fat was calculated from measurements of height, weight, neck circumference, and abdomen circumference using the *Maximum Weight for Height Screen Table* from OPNAVINST 6110.1H. BCA was passed when the participant did not exceed maximum weight for height allowed for age and gender; or 2) if he exceeded the maximum weight for height, but not maximum body fat percentage allowed for age and gender. All military participants had a physical training test score > 80% (top 20%) on their respective military fitness test and engaged in physical training 3 to 4 days per week (self-report). Physical activity could include any form of aerobic or strength training activities or a combination of both, whereby the subject maintained high exercise heart rates during his training. Resting heart rates could not exceed 70 bpm and resting blood pressure could not exceed 139/89 mmHg.

Certain health and behavioral factors were used to exclude individual participants due to potential confounding effects. Specifically, participants were excluded for any of the following reasons: tobacco use during the last 6 months; a history of significant neurological, psychiatric, or sleep-related problems; excessive alcohol use during the last 6 months (i.e., more than 14 drinks per week); regularly consuming more than 200 mg of caffeine per day in the past 6 months; use of any medications and supplements, both prescription and over-the-counter; the inability to complete a 2-mile walk at 3 miles per hour (mph) with a 30-lb backpack once a day for 3 separate days.

Most of the participants were compensated for their time and effort. Those who completed the entire study received a payment of $375. The breakdown of payment was as follows: successful completion of the required amount of sleep for 3 nights at home with activity monitor was $45 ($15/night); completion of in-laboratory portion of the study was $300 ($75/24-hour period); bonus for completion of the entire study was $30. The total amount was determined according to Federal Policy that payment to research subjects must be undertaken with the intent to minimize

the possibility of coercion or undue influence (32 CFR.219.116). Participants were compensated on a prorated per phase basis if they discontinued participation (either by choice or investigator discontinuation), however, all participants completed the study once enrolled in the in-house portion. One participant chose to complete the study without compensation.

2.4 Description of study

Participation in this study took approximately 5 days in the lab plus 3 days at home where sleep was assessed by wrist monitors; participants were required to sleep a minimum of 7 hours per night the 3 nights immediately preceding the laboratory portion of the study. For the in-house portion of the study, participants remained at the Naval Medical Research Unit Dayton (NAMRU-D) research facility throughout the study. They were provided three meals per day plus snacks ad libitum. No caffeine (other than the study dose) was allowed. Otherwise, no dietary restrictions were imposed. Entertainment to fill non-test times included a choice of movies or games, or quiet time reading. At no time other than during personal hygiene was the participant left alone; a staff member was always with the participant. Prior to the sleep-deprivation period, participants spent 2 days in the lab for training on the tasks and for baseline measurements. After the period of sleep deprivation, participants remained in the laboratory for a night of recovery sleep and were then released the morning of Day 5. The daily testing schedule is shown in Table 1 below, with the session test schedule shown in Table 2.

Table 1. Daily testing schedule.

Time	Day 1	Day 2	Day 3	Day 4	Day 5
0000				2mile March	
0200				Test 1	
0500 0545		Wake-up	Wake-up Breath Sample 1	Test 2	
0600		2mile March	2mile March		Wake-up
0745 0800		Training 1	Baseline 1	Breath Sample 4 Test 3	Debrief & Dismiss
1100		Training 2	Baseline 2	Test 4	
1345 1400		Training 3	Breath Sample 2 Baseline 3	Test 5	
1600	Arrive; EEG electrodes, questionnaires				
2000					
2045 2100	Adaptation sleep	Baseline sleep		Breath Sample 5 Bedtime	
2200					
2245 2300			Breath sample 3 **Drug dose**		

Table 2. Session tests schedule.

Time in minutes from beginning of session	Test
00	Depth Perception Test
20	Flight Simulator
45	PMI FIT
50	PVT
60	Go/No-Go / Balloon Risk-Taking Task
75	Resting EEG / Lapse Test
110	POMS / VAS / SE / Vitals (BP / HR / Temp)
120	BREAK

Participants were tested in pairs whenever possible; however, single participant runs were also scheduled. Prior to laboratory data collection, participants' wrist activity data were downloaded and checked for compliance with the time-in-bed requirements prior to entering the in-laboratory portion of the study. Those not meeting this requirement were not enrolled in the in-lab portion of the study until this requirement was met. On the first day of the laboratory portion, participants arrived at the NAMRU-D laboratory at approximately 1600. At this time they completed the NEO-PI-R and Horne and Östberg Morningness/Eveningness questionnaires and electrodes were applied to the participant's scalp. These electrodes remained attached throughout the study in order to measure brain activity during the resting EEG, lapse test, and nightly polysomnography recordings. That night participants were allowed to sleep from 2100 to 0500 on the next day. This first night of sleep in the laboratory was for adaptation to the environment and measures of sleep architecture were recorded via polysomnography, but not analyzed. During the following day (Day 2), participants were trained on each of the cognitive and behavioral tasks 3 times throughout the day, beginning with the 2-mile march at 0600 and ending with the third cognitive test session at approximately 1600. Participants were allowed 8 hours of sleep that night, from 2100 until 0500 the next day. On Day 3 of the study, baseline measures were taken for all of the tasks learned during the previous day. In addition, five breath samples were obtained from a subsample of participants starting at 0545, with additional samples taken at 1345 and 2245 on Day 3, and at 0745 and 2045 on Day 4. Starting their third night in the research facility, participants were not allowed any sleep and completed the same testing sessions that they experienced during the training and baseline days. Additionally, participants completed the 2-mile march with rucksack at 0600 on this day. At 2300 on Day 3, participants received the treatment appropriate for the group to which they were randomly assigned (i.e., placebo, 200mg modafinil, 200mg caffeine, or modafinil + caffeine with water). The elimination half-life of modafinil is approximately 14 hours (sd = 3.2) with a time to peak concentration of approximately 2 hours (Darwish et al, 2010). For caffeine in gum, the elimination half-life is approximately 2-4 hours (however it varies widely) and the time to peak concentration is approximately 1 hour (45 to 80 min) (Kamimori et al, 2002). Thus, it was expected that caffeine would have a shorter duration of efficacy than would modafinil, and this was taken into account

during data analysis and interpretation. After completion of the fifth testing session on Day 4 of the study, participants were allowed 9 hours in bed for recovery sleep. Participants were awakened at 0600, debriefed and dismissed when they felt they had sufficiently recovered.

3.0 RESULTS AND DISCUSSION

A total of 24 individuals enrolled in the study. The data from the wrist activity monitor were used to determine compliance with the sleep requirement that at least 7 hours of sleep occurred for each of the 3 nights prior starting of the in-lab portion of the study. The data from the activity monitors were reviewed for compliance with the sleep requirement on Monday afternoon, the first day of the in-lab portion of the study. Those potential participants who did not sleep at least 7 hours per night were either rescheduled until the sleep requirements were met or dropped from the study. Of the 24 individuals enrolled, 5 did not meet the minimum sleep requirement prior to the in-lab portion of the study and could not reschedule another time to return. Therefore, 19 individuals completed the study. One participant's data indicated poor compliance with testing instructions starting on the baseline day and continuing throughout the rest of the study period; therefore, his data were removed from the data set. He was in the Placebo group. The remaining 18 individuals' data were analyzed for the performance tests during the wake period. The group enrollment with demographic characteristics is shown in Table 3. An analysis of variance for each of the factors was not significant among the groups.

Table 3. Demographics of each group (numbers represent means with ranges in parentheses).

Group	N	Age	Horne-Östberg Morningness/Eveningness Score	NEO-PI-R Neuroticism Score	NEO-PI-R Extraversion Score
Caffeine	5	26.0 (22-33)	46.4 (34-53)	86.8 (69-122)	128.8 (105-150)
Placebo	4	25.4 (21-31)	50.0 (45-55)	69.6 (55-82)	128.2 (112-139)
Modafinil	4	27.4 (22-29)	53.0 (43-66)	68.8 (58-88)	108.0 (77-124)
Modafinil+Caffeine	5	26.0 (21-32)	56.2 (39-65)	76.8 (41-121)	113.6 (70-151)

Preliminary analyses of the performance data indicated differences among the groups for the baseline sessions. To adjust for these group differences, an average score from the three baseline sessions was calculated and each testing score from each of the cognitive tasks were subtracted from the average baseline score (baseline - session) to give a difference score for each session. These difference scores were analyzed with a mixed-model analysis of variance (ANOVA), with treatment condition as the grouping factor and session as the repeated factor. The alpha level was set at .05. Significant interaction effects were followed up with simple effects and post hoc analyses. Significant condition main effects were followed up with Unequal N Honestly Significant Difference (HSD) and significant session effects were followed up with Tukey HSD test to determine differences between means. The Statistica 64© Version 12 statistical software

package (StatSoft, Inc., Tulsa OK) was used to analyze the data. Graphs of the data were reversed (negative up) in order to show an intuitive picture of the data, i.e., an increase in measurement is shown as an upward trend on the graph with a decrease indicated by downward trends. Graphs depict group means with standard error bars.

3.1 Prestudy questionnaires and assessments.

Personality and circadian type questionnaires were administered prior to data collection in order to determine whether any of the participants were extreme morning or evening types and to quantify certain personality factors (e.g., neuroticism, extraversion).

3.1.1 The Horne and Östberg Morningness/Eveningness Questionnaire was used to subjectively evaluate each participant's circadian type. A one-way ANOVA revealed no differences among the groups for the Morningness-Eveningness score ($F(3,15) = 1.290$, $p = .331$, $\eta_p^2 = .205$). Means and ranges for each group are shown in Table 3.

3.1.2 The factors from the Revised NEO Personality Inventory (NEO-PI-R) were each analyzed with a one-way ANOVA. No significant differences occurred among the groups on the two domains of interest: Neuroticism ($F(3,15) = 0.764$, $p = .372$, $\eta_p^2 = 0.133$) and Extraversion ($F(3,15) = 1.120$, $p = .372$, $\eta_p^2 = .183$). The group means and ranges are shown in Table 3.

3.2 Performance tests and questionnaires.

3.2.1 Mood and side effects assessments. Mood was measured with two questionnaires, the Profile of Mood States (POMS) and Visual Analogue Scale (VAS). Side effects were measured with a questionnaire presented immediately after the mood questionnaires at the end of each testing session.

3.2.1.1 All six factors from the *POMS*, as well as the Total Mood Disturbance score, were analyzed with a mixed-model ANOVA. The results from these analyses are presented below.

The analysis indicated a significant interaction between group and session for the *Fatigue* factor ($F(4,52) = 1.993$, $p = .044$, $\eta_p^2 = 0.315$). Follow-up analyses indicated reports of higher fatigue at 1400 than at 0200 in the Modafinil group, and a tendency for the Caffeine/Modafinil group to report higher fatigue at the 1100 session than at the 0200 session ($p = .069$), but none of the other groups showed meaningful changes across the sessions. These effects are illustrated in Figure 10.

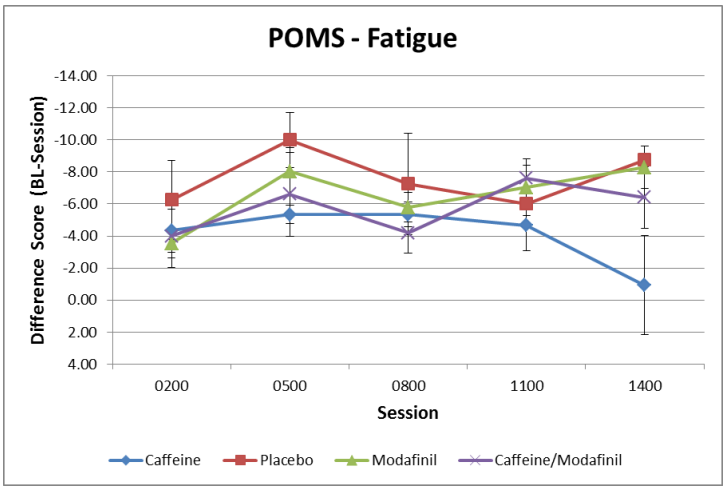

Figure 10. Interaction effect between condition and session.

A main effect for session ($F(4,52) = 2.491$, $p = .054$, $\eta_p^2 = 0.161$) occurred, but follow-up analysis showed only a tendency for fatigue to be lower at the 0200 session than at the 0500 session ($p = .063$). These effects are illustrated in Figure 11.

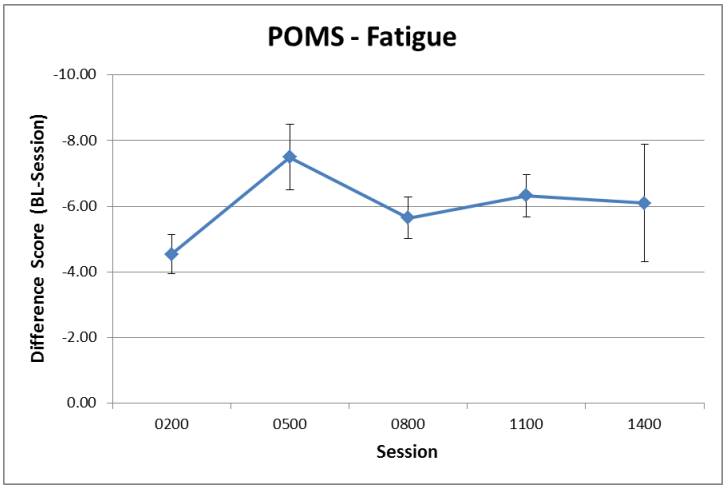

Figure 11. Session effect for POMS Fatigue score.

The ANOVA for the *Vigor* factor did not show any interactions, but did indicate a main effect for condition ($F(3,14) = 3.516$, $p = .044$, $\eta_p^2 = .430$). Follow-up analysis revealed higher vigor scores for the Caffeine/Modafinil group than for the Placebo group ($p = .046$), with no differences between any of the other groups. This effect is shown in Figure 12. There was no session main effect for this factor.

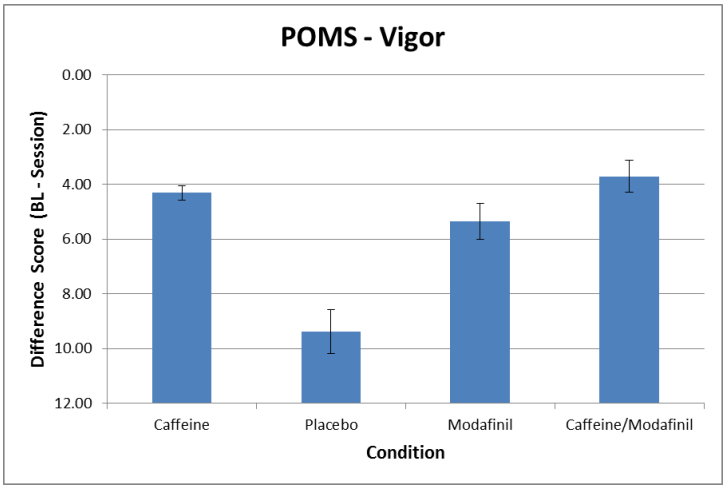

Figure 12. Condition main effect for POMS Vigor score.

The ANOVA for the *Depression* factor revealed an interaction effect between condition and session ($F(12,56) = 2.013$, $p = .040$, $\eta_p^2 = .301$). The scores in the Caffeine group were higher at the 0200 session than at the 1400 session ($p = .027$). No other effects across the sessions occurred within any of the other groups. This effect is illustrated in Figure 13.

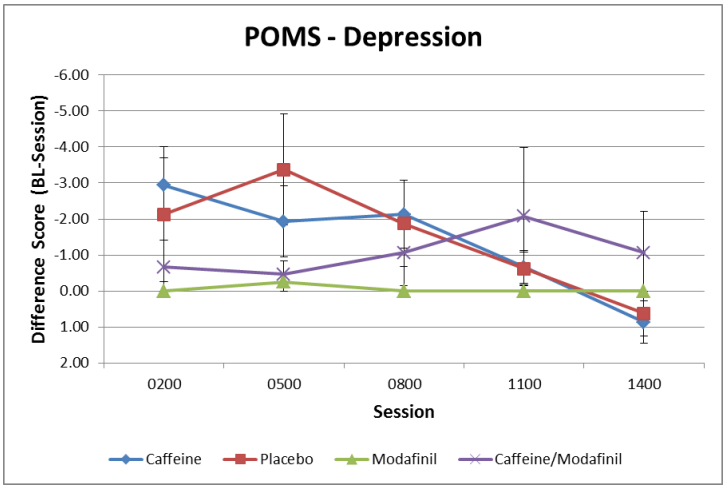

Figure 13. Interaction between group and session for the POMS Depression factor.

A main effect for session ($F(4,56) = 3.181$, $p = .020$, $\eta_p^2 = 0.185$) indicated higher subjective depression at the 0200 and 0500 session than at the 1400 session ($p = .036$ for both comparisons). This effect is shown in Figure 14.

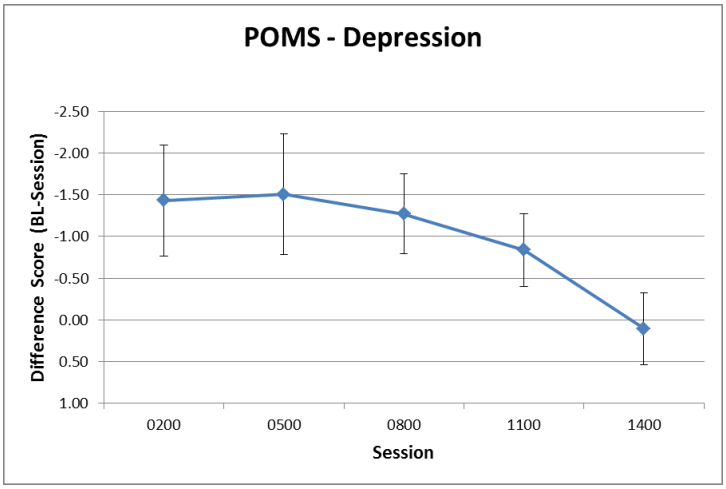

Figure 14. Session main effect for POMS Depression factor.

ANOVAs for the other factors of *Tension*, *Anger*, and *Confusion* did not indicate any differences among the groups or across time. Statistical summary results for all POMS factors are presented in Table 4.

Table 4. Summary statistics for all the factors from the POMS.

Factor	Effect	F (df)	p	η_p^2
Fatigue[#]	Condition x Session Interaction	F(12,52) = 1.993	**.044**	.315
	Condition Main Effect	F(3,13) = 1.762	**.021**	.289
	Session Main Effect	F(4,52) = 2.490	**.054**	.161
Vigor	Condition x Session Interaction	F(12,56) = 1.524	.143	.246
	Condition Main Effect	F(3,14) = 3.516	**.044**	.430
	Session Main Effect	F(4,56) = 1.524	.143	.246
Tension	Condition x Session Interaction	F(12,56) = 0.413	.952	.081
	Condition Main Effect	F(3,14) = 0.795	.517	.146
	Session Main Effect	F(4,56) = 0.350	.843	.024
Depression	Condition x Session Interaction	F(12,56) = 2.013	**.040**	.301
	Condition Main Effect	F(3,14) = 0.786	.521	.144
	Session Main Effect	F(4,56) = 3.181	**.020**	.185
Anger	Condition x Session Interaction	F(12,56) = 1.343	.221	.224
	Condition Main Effect	F(3,14) = 0.429	.735	.084
	Session Main Effect	F(4,56) = 1.792	.143	.113
Confusion	Condition x Session Interaction	F(12,56) = 0.678	.765	.127
	Condition Main Effect	F(3,14) = 1.229	.336	.208
	Session Main Effect	F(4,56) = 1.537	.204	.099
TMD Score	Condition x Session Interaction	F(12,56) = 2.194	**.024**	.320
	Condition Main Effect	F(3,14) = 4.300	**.024**	.480
	Session Main Effect	F(4,56) = 2.194	**.046**	.320

[#]1 session missing from data set

When all factors were combined into a *Total Mood Disturbance (TMD) score*, an interaction between condition and session occurred ($F(12,56) = 2.194$, $p = .024$, $\eta_p^2 = .320$). The Modafinil group reported a lower score at the 0200 session than at all the other sessions (all p-values < .03). No other groups showed any significant changes across time. However, analysis comparing groups at each session indicated higher mood disturbance in the Placebo group at the 0500 session than any other groups (all p-values < .02). There was a tendency for the Placebo group to have a higher mood disturbance score than the Modafinil group at the 0200 session ($p = .064$) and higher than the Caffeine/Modafinil group at the 0800 session ($p = .057$). This effect is illustrated in Figure 15.

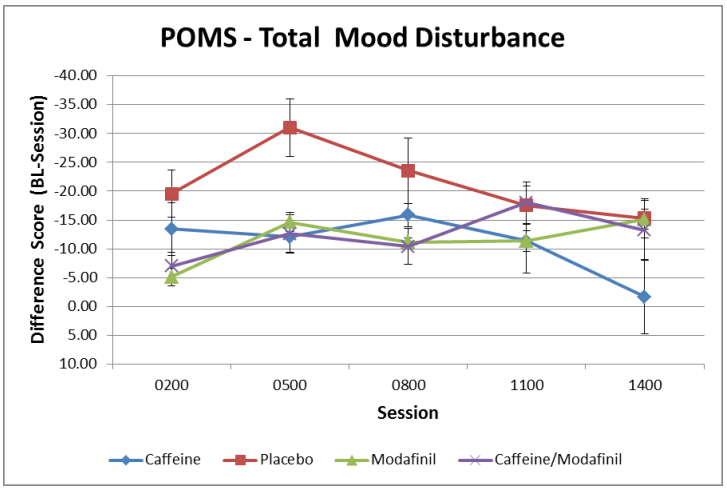

Figure 15. Interaction effect between condition and session for the POMS Total Mood Disturbance (TMD) score.

There was a main effect for condition ($F(3,14) = 4.299$, $p = .024$, $\eta_p^2 = .480$). The post hoc test indicated that those in the Placebo group had higher TMD scores than those in the Caffeine group ($p = .035$). There was a tendency for the Placebo group to have higher TMD scores than those in the Modafinil group ($p = .058$) and in the Caffeine/Modafinil group ($p = .086$). These effects are shown in Figure 16.

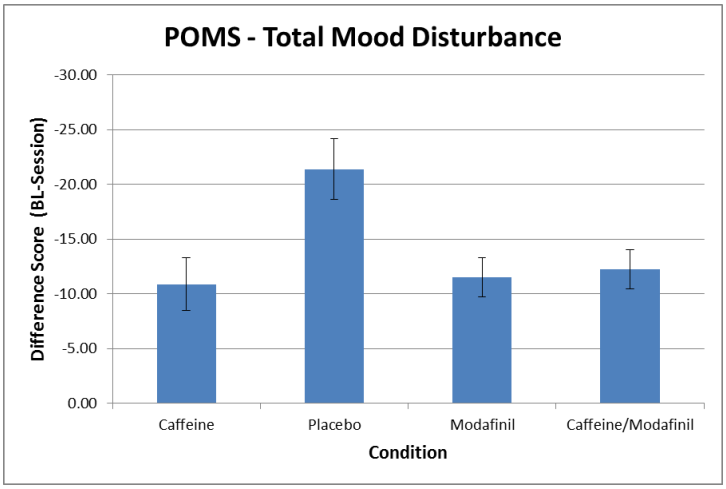

Figure 16. Group main effect for the POMS Total Mood Disturbance score.

A main effect for session occurred for the TMD score ($F(4,56) = 2.594$, $p = .046$, , $\eta_p^2 = .156$), however, follow-up analyses did not reveal a significant difference between any of the sessions. There was a tendency for the 0500 session to show a lower TMD score than the 1400 session ($p = .083$). The change across the sessions is shown in Figure 17.

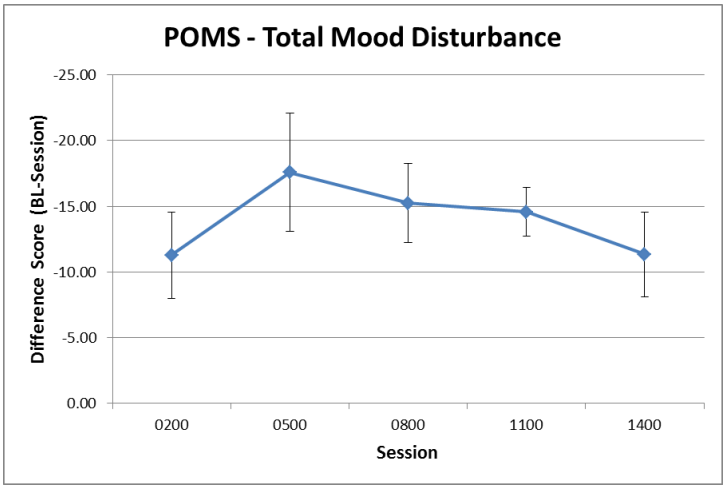

Figure 17. Session main effect for the POMS Total Mood Disturbance score.

3.2.1.2 The variables from the *VAS* were analyzed with a mixed-model ANOVA. Each variable was analyzed separately.

A significant interaction between condition and session was shown for Alert ($F(12,56) = 2.100$, $p = .032$, $\eta_p^2 = 0.310$). Analysis of simple effects indicated the Placebo and Modafinil groups showed significant changes across time. Participants in the Placebo group reported lower levels of alertness at the 0500 session than at the 1100 session ($p = .045$). People in the Modafinil group reported higher levels of alertness at the 0200 session than at the 1100 and 1400 sessions ($p = .011$ and .001, respectively), and higher alertness at the 0800 session than at the 1400

session (p = .023). None of the other groups showed a significant change across time. When comparing the groups at each test session, the analysis revealed differences among the groups at 0200 with the Modafinil group reporting significantly more alertness than the Placebo group. There was a tendency for the groups to differ at 0500 (p = .067), with the Modafinil group reporting higher alertness than the Placebo group. No other differences among the groups occurred at any other session. Figure 18 shows the changes from baseline among the groups at each session. No other variables from the VAS showed a significant interaction between group and session.

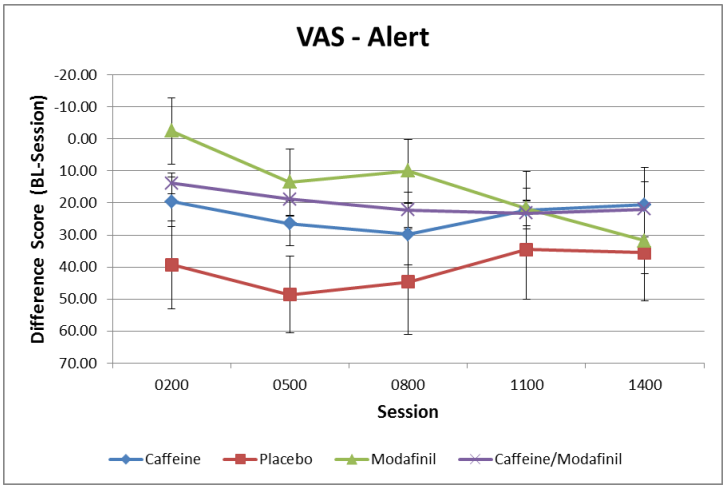

Figure 18. Interaction between group and session for the VAS Alert factor.

There was no main effect for condition for the Alert factor, but there was a main effect for session ($F(4,56) = 2.100$, $p = .032$, $\eta_p^2 = .165$). Post hoc analyses showed only a tendency for the 0200 session to have lower alertness scores than those at the 0500 session (p = .092), the 0800 session (p = .080), and the 1400 session (p = .069). This effect is illustrated in Figure 19.

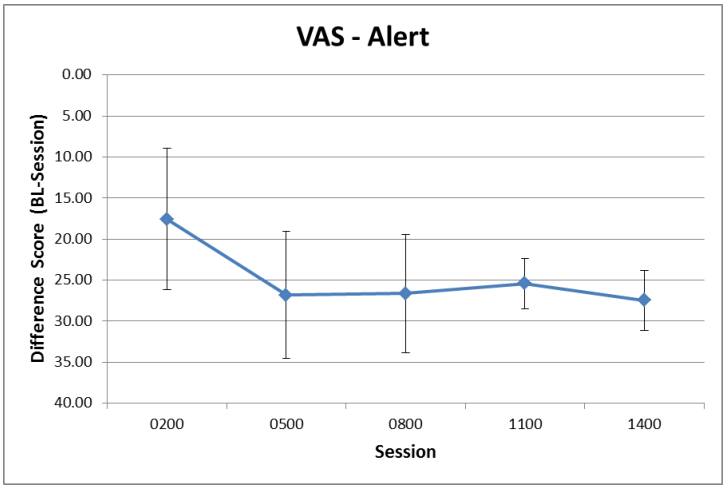

Figure 19. Session effect for the VAS Alert factor.

The ANOVA for the Jittery factor revealed only a condition main effect, with the Caffeine group reporting lower levels of jitteriness than the Modafinil group (p = .050). This effect is illustrated in Figure 20.

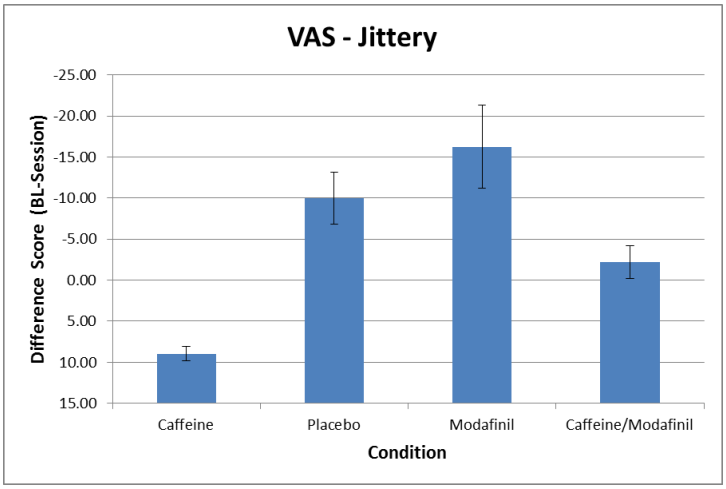

Figure 20. Group main effect for VAS Jittery factor.

The ANOVA revealed only a main effect for session for the factor Anxious ($F(4,56) = 3.362$, $p = .015$, $\eta_p^2 = 0.194$). Further investigation revealed that participants reported lower levels of anxiety at the 0500 session than at the 1400 session (p = .048). There was a tendency for lower levels of anxiety at the 0200 session than at the 1400 session (p = .061) and lower reported anxiety at the 1100 session than at the 1400 session (p = .053). This effect is shown in Figure 21.

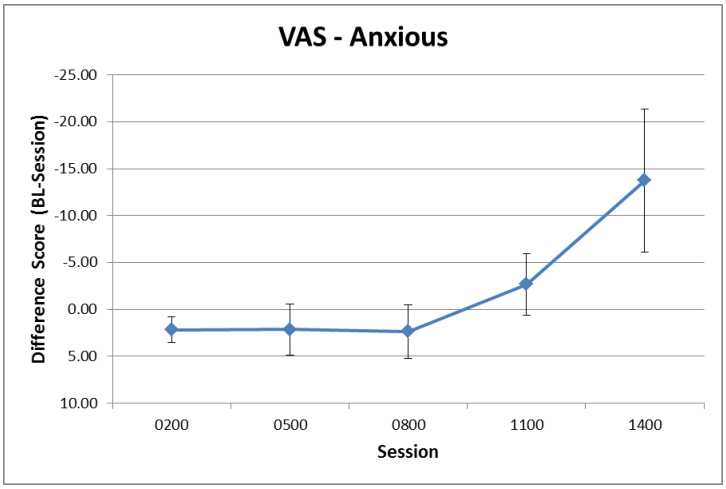

Figure 21. Session main effect for VAS Anxious factor.

The ANOVA did not indicate a significant interaction or condition main effect for the Energetic factor. However, there was a tendency for a session main effect ($F(4,56) = 2.417$, $p = .059$, $\eta_p^2 = 0.147$). There was a tendency for the scores to be higher during the 0200 session than during the 0500 session (p = .073). This effect is shown in Figure 22.

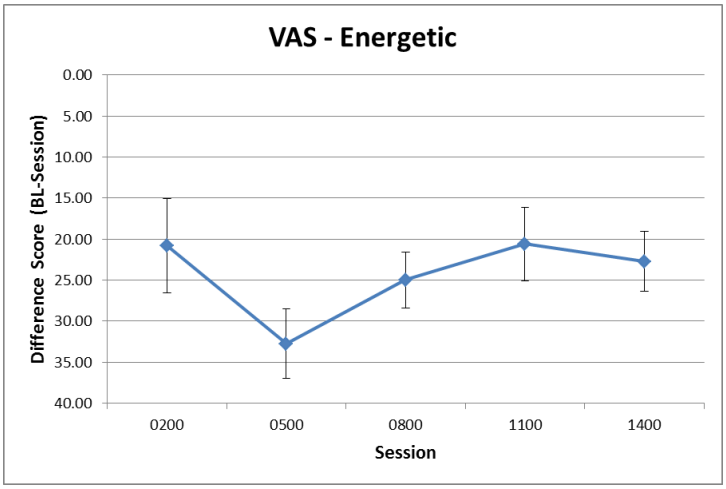

Figure 22. Session main effect for the VAS Energetic factor.

The variables Confident, Irritable, Sleepy and Talkative did not show a statistically significant difference for the group by session interaction or main effects for condition and session. A summary of each of the factors from the VAS is presented in Table 5.

3.2.1.3 Responses for each item on the *side-effects questionnaire* were tallied and results summarized by group. Baseline day sessions were added to give total responses for the day (3 responses from each individual), and deprivation day sessions were added to give total responses for the day (5 responses from each individual). More than one response per individual is possible for each of the days summarized. For example, the side effect "anxiety" had three responses for "Slight/Moderate" in the Caffeine group on the Baseline day, but these three responses were from one individual. There were 7 responses in the Placebo group on the Deprivation days, but these responses came from only 3 individuals. Only the relevant side effects are reported in Table 6.

Table 5. Summary statistics for all the factors from the VAS.

Factor	Effect	F (df)	p	η_p^2
Alertness	Condition x Session Interaction	F(12,56) = 2.100	**.032**	.310
	Condition Main Effect	F(3,14) = 1.396	.285	.230
	Session Main Effect	F(4,56) = 2.764	**.036**	.165
Anxious	Condition x Session Interaction	F(12,56) = 0.825	.624	.150
	Condition Main Effect	F(3,14) = 1.929	.171	.292
	Session Main Effect	F(4,56) = 3.362	**.015**	.194
Energetic	Condition x Session Interaction	F(12,56) = 1.705	.090	.268
	Condition Main Effect	F(3,14) = 0.466	.711	.091
	Session Main Effect	F(4,56) = 2.417	.059	.147
Confident	Condition x Session Interaction	F(12,56) = 1.409	.189	.232
	Condition Main Effect	F(3,14) = 0.718	.557	.133
	Session Main Effect	F(4,56) = 1.164	.336	.077
Irritable	Condition x Session Interaction	F(12,56) = 1.472	.163	.240
	Condition Main Effect	F(3,14) = 1.415	.280	.233
	Session Main Effect	F(4,56) = 0.820	.518	.055
Jittery	Condition x Session Interaction	F(12,56) = 1.121	.362	.194
	Condition Main Effect	F(3,14) = 3.533	**.043**	.431
	Session Main Effect	F(4,56) = 1.611	.184	.103
Sleepy	Condition x Session Interaction	F(12,56) = 1.538	.138	.248
	Condition Main Effect	F(3,14) = 2.014	.158	.301
	Session Main Effect	F(4,56) = 2.035	.102	.127
Talkative	Condition x Session Interaction	F(12,56) = 1.135	.352	.120
	Condition Main Effect	F(3,14) = 1.431	.276	.235
	Session Main Effect	F(4,56) = 0.321	.863	.022

Table 6. Side effects questionnaire responses for select questions.

	Baseline Days				Deprivation Days			
Anxiety	Caffeine (n = 5)	Placebo (n = 4)	Modafinil (n = 4)	Modafinil + Caffeine (n = 5)	Caffeine (n = 5)	Placebo (n = 4)	Modafinil (n = 4)	Modafinil + Caffeine (n = 5)
None	12	12	11	14	19	13	20	18
Slight/Mild	3*	0	0	1	4+	7^	2*	4*
Moderate/Severe	0	0	0	0	2+	0	0	1

*1 individual; +1 individual reported 5 of the incidences in these 2 categories; ^3 individuals

	Baseline Days				Deprivation Days			
Irritability	Caffeine (n = 5)	Placebo (n = 4)	Modafinil (n = 4)	Modafinil + Caffeine (n = 5)	Caffeine (n = 5)	Placebo (n = 4)	Modafinil (n = 4)	Modafinil + Caffeine (n = 5)
None	12	6	10	10	15	7	17	15
Slight/Mild	3*	4^	1	5^	8+	9+	2*	8^
Moderate/Severe	0	2*	0	0	2	4	0	0

*1 individual; +4 individuals reported at least 1 symptom; +3 individuals; ^2 individuals

	Baseline Days				Deprivation Days			
Tremor	Caffeine (n = 5)	Placebo (n = 4)	Modafinil (n = 4)	Modafinil + Caffeine (n = 5)	Caffeine (n = 5)	Placebo (n = 4)	Modafinil (n = 4)	Modafinil + Caffeine (n = 5)
None	15	12	11	15	25	19	17	23
Slight/Mild	0	0	0	0	0	1	2*	0
Moderate/Severe	0	0	0	0	0	0	0	0

*1 individual

	Baseline Days				Deprivation Days			
Headache	Caffeine (n = 5)	Placebo (n = 4)	Modafinil (n = 4)	Modafinil + Caffeine (n = 5)	Caffeine (n = 5)	Placebo (n = 4)	Modafinil (n = 4)	Modafinil + Caffeine (n = 5)
None	12	10	11	15	19	15	19	23
Slight/Mild	3*	2*	0	0	6+	5*	0	0
Moderate/Severe	0	0	0	0	0	0	0	0

*1 individual; +2 individuals, with 1 reporting 5 symptoms

	Baseline Days				Deprivation Days			
Nausea	Caffeine (n = 5)	Placebo (n = 4)	Modafinil (n = 4)	Modafinil + Caffeine (n = 5)	Caffeine (n = 5)	Placebo (n = 4)	Modafinil (n = 4)	Modafinil + Caffeine (n = 5)
None	15	12	11	15	20	19	19	21
Slight/Mild	0	0	0	0	5*	1	0	2+
Moderate/Severe	0	0	0	0	0	0	0	0

*1 individual; +2 individuals

	Baseline Days				Deprivation Days			
Rapid Heart Beat	Caffeine (n = 5)	Placebo (n = 4)	Modafinil (n = 4)	Modafinil + Caffeine (n = 5)	Caffeine (n = 5)	Placebo (n = 4)	Modafinil (n = 4)	Modafinil + Caffeine (n = 5)
None	15	12	11	15	24	20	18	22
Slight/Mild	0	0	0	0	1	0	1	1
Moderate/Severe	0	0	0	0	0	0	0	0

3.2.2 Cognitive tests. A series of cognitive measures were evaluated to determine effects of sleep loss as well as treatment conditions on measures including reaction time, inhibition control, risk taking tendency, and tracking performance. The results from the mixed model ANOVA for each of the tests are described below.

3.2.2.1 Flight simulator performance was analyzed from the final 20 minutes of the 25-minute flight. Accuracy was measured for altitude, heading, and airspeed using root mean square error (RMSE). No significant interaction between group and session occurred for any of the measures of flight performance, nor was there a main effect for condition. However, the ANOVA revealed a difference across time for altitude ($F(4,56) = 3.144$, $p = .021$, $\eta_p^2 = 0.183$) with post hoc analyses indicating the 0200 session had better performance than the 1100 session ($p = .009$). A similar effect was found with airspeed ($F(4,56) = 6.685$, $p = .0002$, $\eta_p^2 = 0.323$), with post hoc analysis showing better performance at the 0200 session than performance at the 0800, 1100, and 1400 sessions ($p = .001$, .0004, and .018, respectively). No significant effects occurred for heading. Figure 23 illustrates the effects.

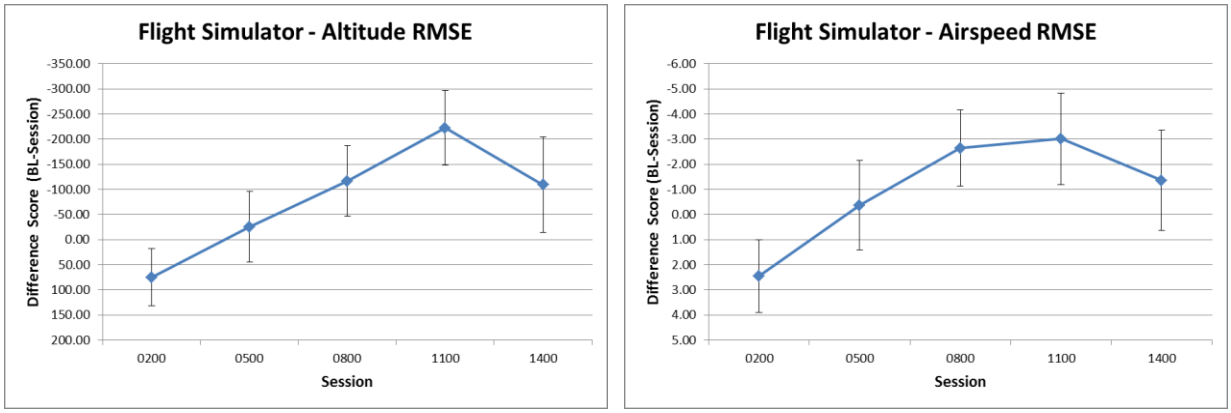

Figure 23. Session main effect for Altitude and Airspeed for the flight simulator.

3.2.2.2 The variables analyzed from the *Psychomotor Vigilance Test (PVT)* were mean reciprocal reaction time (RRT), the 10% fastest reciprocal reaction times (FRRT), the 10% slowest reciprocal reaction times (SRRT), and number of lapses (RTs equal to 500 msec or more). A significant interaction between condition and session was not revealed for any of the variables. However, the ANOVA revealed a significant condition main effect for lapses ($F(3,14) = 5.353$, $p = .011$, $\eta_p^2 = .534$), RRT ($F(3,14) = 5.801$, $p = .009$, $\eta_p^2 = .554$), FRRT ($F(3,14) = 4.358$, $p = .023$, $\eta_p^2 = .483$), and SRRT ($F(3,14) = 5.132$, $p = .013$, $\eta_p^2 = .524$). Post hoc analyses showed fewer lapses in the Caffeine/Modafinil group than for the Placebo ($p = .036$) and Caffeine ($p = .031$) groups. The Caffeine/Modafinil group had faster overall reaction times than the Placebo group ($p = .012$), with a tendency to be faster than the Caffeine group ($p = .068$) and the Modafinil group ($p = .075$). The analysis of the fastest reaction times (FRRT) showed faster responses in the Caffeine/Modafinil group than in the Placebo group ($p = .048$) and a tendency for faster times than the Caffeine group ($p = .085$). When analyzing the slowest reaction times (SRRT), the Caffeine/Modafinil group's reaction time was faster than the Placebo group ($p = .020$). The Modafinil group tended to be faster than the Placebo group, but this effect was not statistically significant ($p = .079$). These results are illustrated in Figure 24.

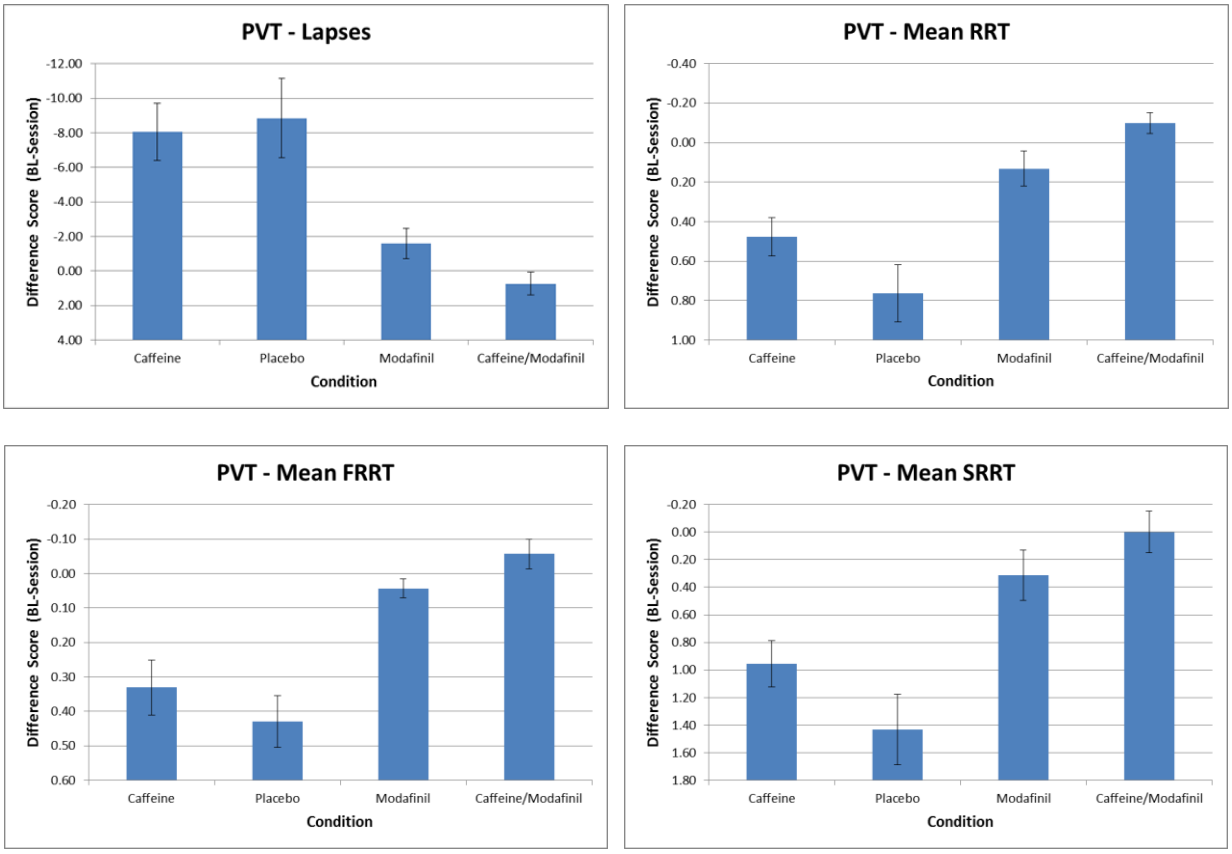

Figure 24. Condition main effects for lapses, RRT, FRRT, and SRRT from the PVT.

The ANOVA revealed a session main effect for number of lapses ($F(4,56) = 3.919$, $p = .007$, $\eta_p^2 = .219$), RRT ($F(4,56) = 6.549$, $p = .0002$, $\eta_p^2 = .319$), FRRT ($F(4, 56) = 3.822$, $p = .008$, $\eta_p^2 = .214$), and SRRT ($F(4,56) = 9.034$, $p < .0001$, $\eta_p^2 = .392$). All measures except the FRRT showed better performance at the 0200 session than any of the other sessions (all p-values < .04); FRRT showed better performance at the 0500 session than at the 1400 session only ($p = .005$). Figure 25 shows all these effects.

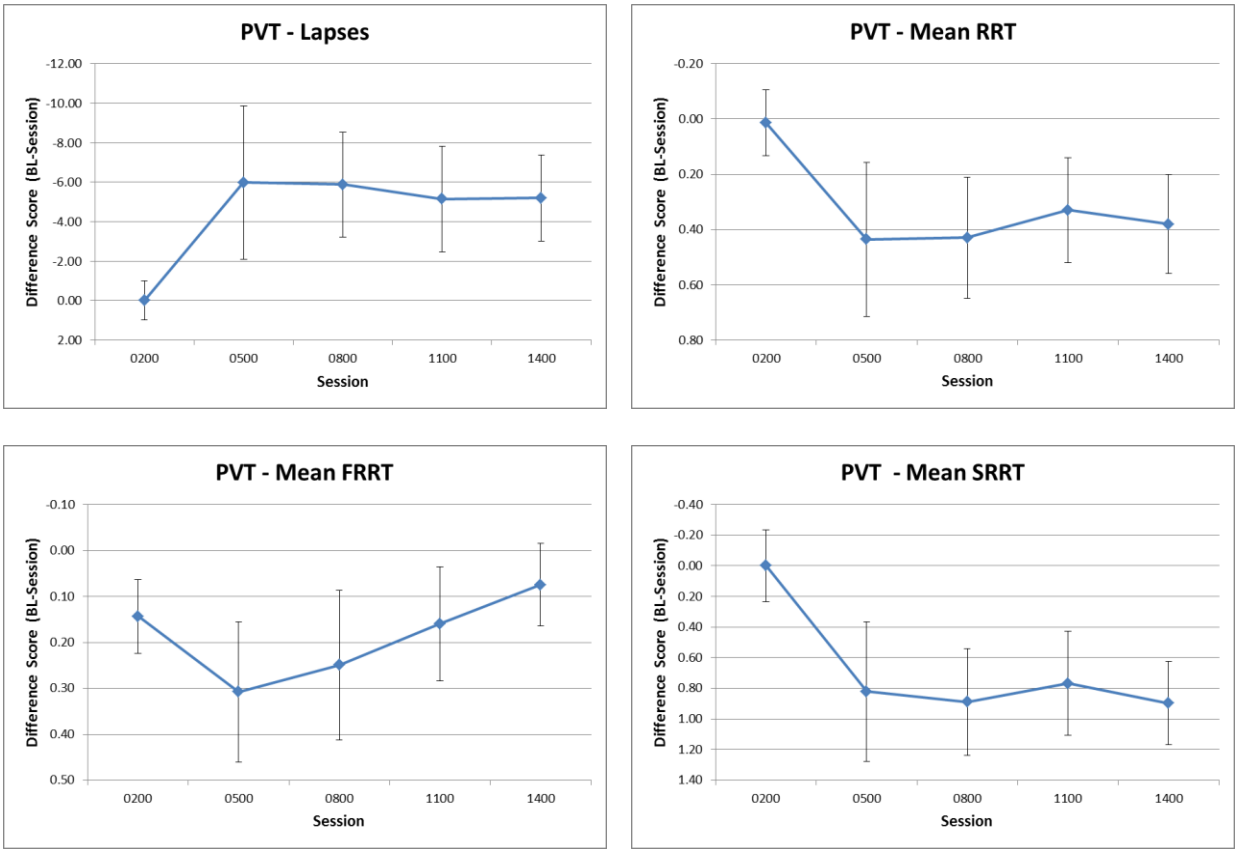

Figure 25. Session main effects for lapses, RRT, FRRT, and SRRT from the PVT.

3.2.2.3 Variables analyzed from the *Go/No-Go task* were hit rate (correct responses), reaction time for correct responses (RTCR), commission errors (responses to the incorrect stimulus), and reaction time for commission errors (RTCE).

The analysis of hit rate indicated a main effect for session ($F(4,56) = 3.096$, $p = .023$, $\eta_p^2 = .181$), with post hoc analysis indicating better performance at the 0200 session than at the 0500 session ($p = .024$). There was no interaction between condition and session or main effect for condition for this measure. The session main effect is shown in Figure 26.

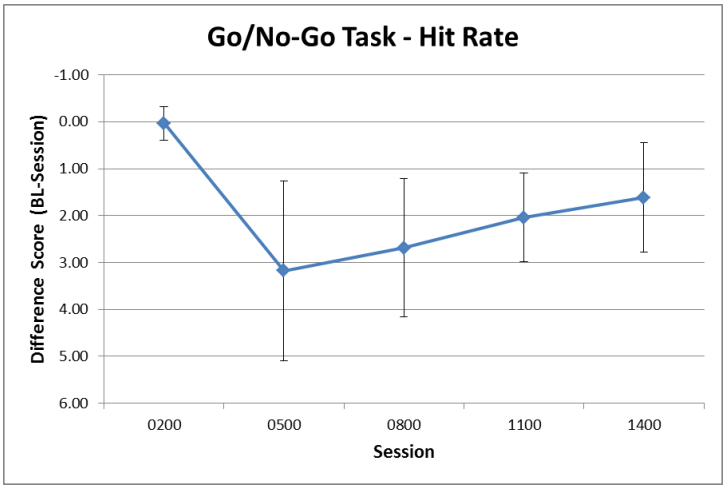

Figure 26. Session main effect for Hit Rate in the Go/No-Go task.

The ANOVA for the RTCR revealed a signification interaction between condition and session ($F(12,56) = 2.641$, $p = .007$, $\eta_p^2 = .361$). Follow-up analyses indicated better performance for the Caffeine/Modafinil group than the Placebo group at the 0500 session, with a tendency for the Caffeine/Modafinil group to have better performance at the 0500 session than the Modafinil group ($p = .091$) and the Caffeine group ($p = .087$). Though not statistically significant, there was a tendency for the Caffeine/Modafinil group to have better performance than the Modafinil group at the 1400 session ($p = .083$). There were differences in performance across the sessions for most of the groups. The Placebo group showed better performance at the 0200 session than at all other sessions ($p < .05$ for each comparison); the Caffeine group showed better performance at the 0200 session than at the 1400 session ($p = .018$), as did the Modafinil group ($p = .030$). The Caffeine/Modafinil group did not show any significant changes in performance across the sessions. Figure 27 illustrates the group differences across time.

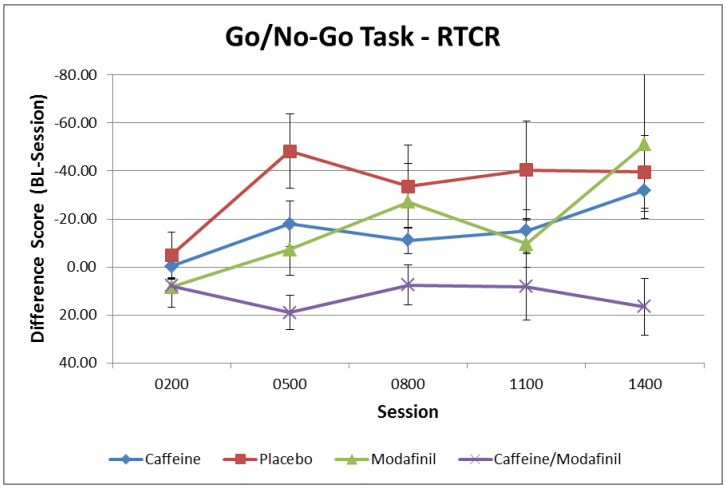

Figure 27. Interaction between condition and session for RTCR from the Go/No-Go Task.

A main effect for condition occurred for RTCR ($F(3,14) = 3.477$, $p = .045$, $\eta_p^2 = .427$) with the Caffeine/Modafinil group showing better performance than the Placebo group ($p = .045$). A

main effect for session also occurred ($F(4,56) = 6.866$, $p < .001$, $\eta_p^2 = .329$), with better performance at the 0200 session than at the 0800, 1100, and 1400 sessions ($p = .026$, .049, and .0002, respectively). The effect between the 0200 session and the 0500 session did not reach statistical significance ($p = .075$). Figure 28 shows both of these effects.

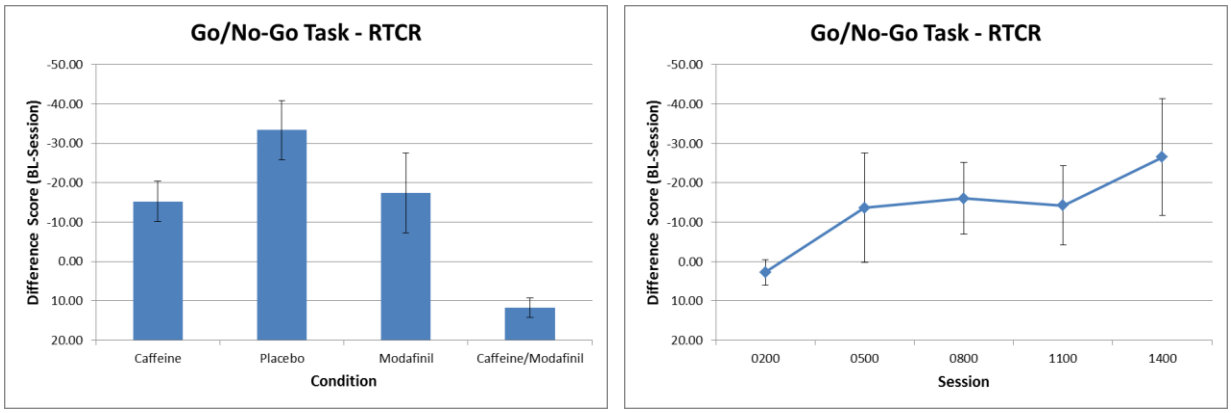

Figure 28. Condition and session main effects for RTCR from the Go/No-Go task.

3.2.2.4 Variables from the *Balloon Analogue Risk Task (BART)* were the number of times the balloon popped, the adjusted average number of pumps (the mean number of pumps for which the balloon did not pop), total score (the total number of points accumulated from unpopped balloons), and the cost/benefit ratio (number of exploded balloons / total number of balloons presented (20 in this study). Of these variables, the ANOVA revealed only a significant interaction between condition and session for the adjusted number of pumps ($F(12,56) = 2.392$, $p = .014$, $\eta_p^2 = .339$). Further analysis indicated performance changes across the session for the Modafinil group, with significantly more pumps at the 1400 session than at the 0500 and 0800 sessions ($p = .009$ and .048, respectively). Figure 29 illustrates this effect.

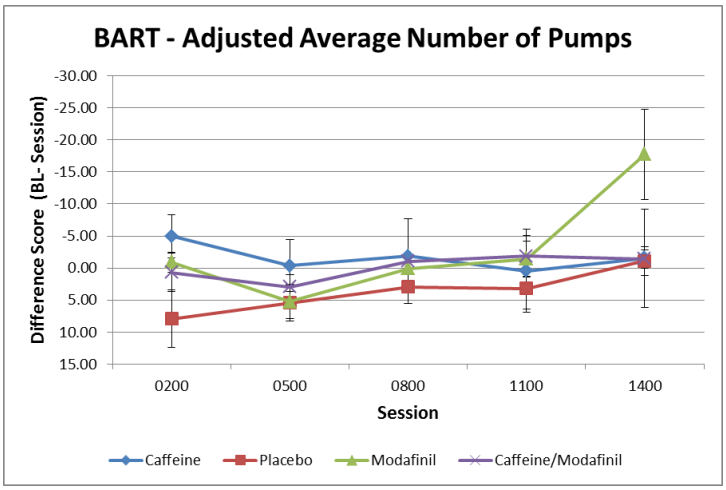

Figure 29. Condition by session interaction for the adjusted average number of pumps from the BART.

The adjusted average number of pumps also showed a significant main effect for session ($F(4,56) = 5.538$, $p = .001$, $\eta_p^2 = .283$). Post hoc analyses showed fewer pumps at the 0200 and 0500 sessions compared to the 1400 session ($p = .050$ and .001, respectively). Figure 30 shows this effect.

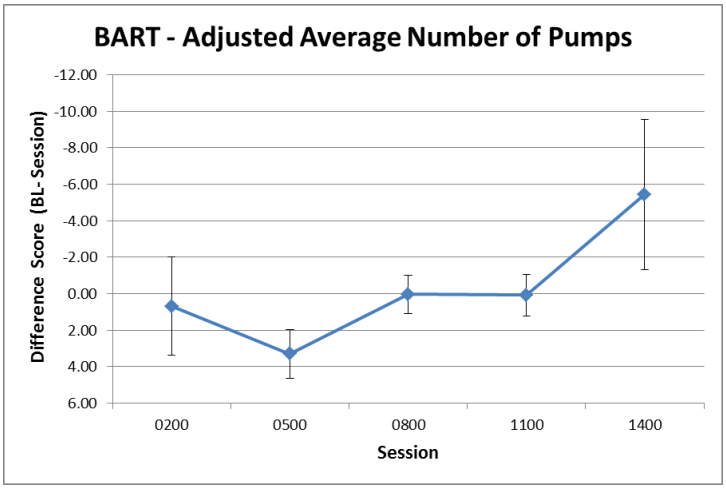

Figure 30. Session effect for the adjusted number of pumps from the BART.

There was no condition main effect for the adjusted number of pumps. None of the other metrics taken from the BART showed any statistically significant interactions or main effects.

3.2.3 Physiological Assessments. Several physiological assessments were obtained to determine the effects of wakefulness and treatment condition on the measures.

3.2.3.1 The *oculometrics* collected with the PMI FIT 2000 included measures of saccadic velocity, pupil diameter, pupil constriction amplitude, and pupil constriction latency, each of which were analyzed separately with the mixed-model ANOVA. Results did not show an interaction between condition and session or a main effect for condition for any of the measures. However, a main effect for session was revealed for saccadic velocity ($F(4,48) = 3.042$, $p = .026$, $\eta_p^2 = .202$), latency ($F(4,48) = 3.403$, $p = .016$, $\eta_p^2 = .221$), and diameter ($F(4,48) = 3.722$, $p = .010$, $\eta_p^2 = .237$). Further analyses indicated a tendency for saccadic velocity to be faster at the 1400 session than at the 0500 session ($p = .064$) and the 1100 session ($p = .088$). There was also a tendency for saccadic velocity to be faster at the 1100 session than the 1400 session ($p = .089$). Latency was significantly slower at the 0500 session than at 0800 session ($p = .005$); diameter was significantly larger at the 0200 than at the 0800 session ($p = .011$) and at the 1400 session ($p = .012$). Figure 31 shows these effects.

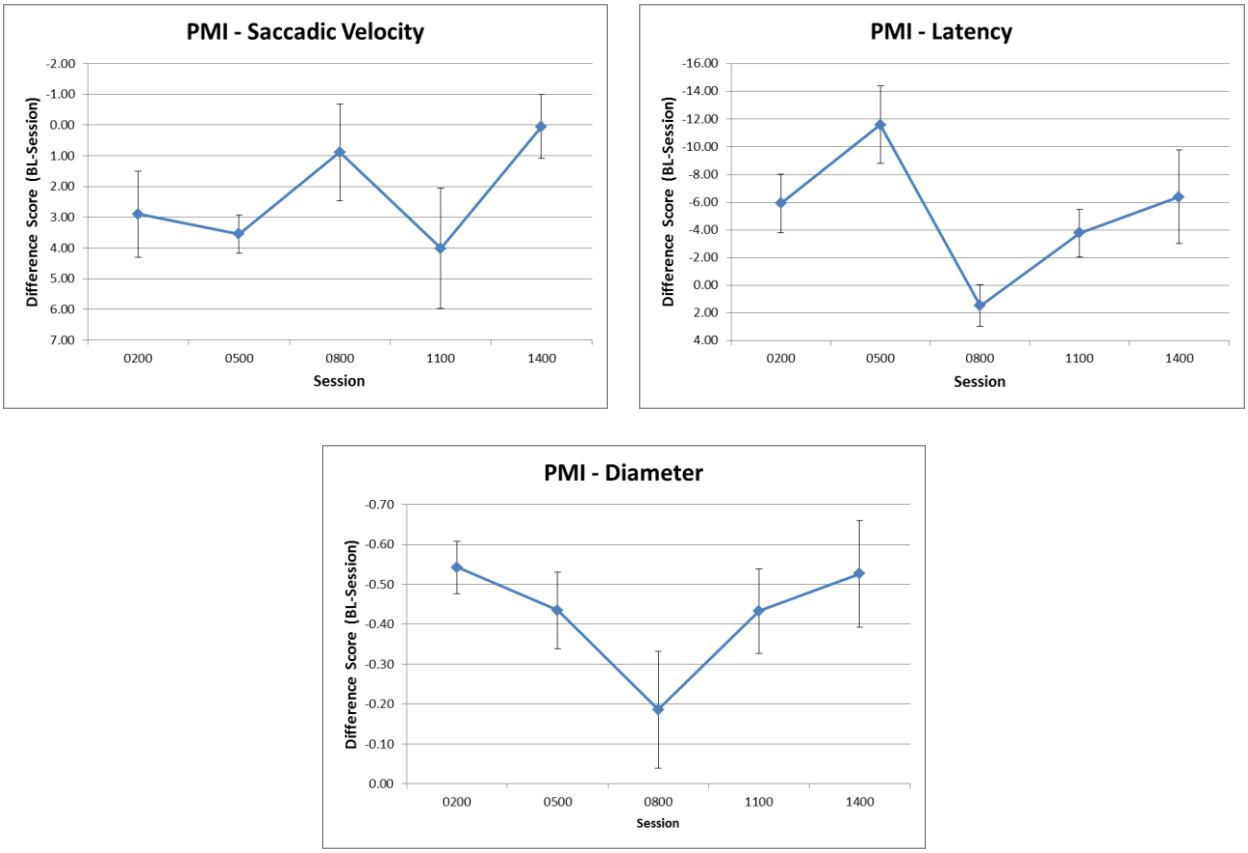

Figure 31. Session main effect for saccadic velocity, latency, and diameter from the PMI FIT.

3.2.3.3 Electroencephalogram (EEG) recordings. Resting EEGs during eyes closed and eyes open were collected during each session of the study. Due to excessive noise in the signal, one participant's data (from the Modafinil group) could not be analyzed for any of the sessions. Data were missing for several sessions for some electrode sites due to excessive noise. The remaining data were analyzed with a mixed-model repeated measures ANOVA with session (1-5) as the repeated factors and condition as the grouping factor. Eyes closed data were analyzed separately from eyes open data. From each of the 2-minute segments of resting EEG, three artifact-free 3-second epochs were selected which represented the gestalt of the 2 minutes and used to calculate absolute power of delta, theta, alpha, and beta activity using a Fast Fourier (FFT) analysis. The FFT used a 256 block Hamming window with a .25 overlap. The DC component was removed. The absolute power from each of the FFTs was grouped into the traditional frequency bands of delta (0.5 – 3.5 Hz), theta (4.0 -7.5 Hz), alpha (8.0 – 12.5 Hz), and beta (13 – 30 Hz). Power from each band was converted to percent power ((delta power/total power) *100) to allow individuals' data to be compared. As with the other data from this study, the three sessions from the baseline day were averaged to yield a common baseline score. The data from each session during the deprivation period were then subtracted from the baseline score to yield a difference-from-baseline score for each session. For this report, only the midline electrodes (Fz, Cz, and Pz) are presented.

The analysis of the *delta band* during eyes open did not show an interaction effect between condition and session. However, a main effect for condition occurred at site Fz ($F(3,11) = 13.480$, $p < .001$, $\eta_p^2 = .786$) with post hoc analysis showing more delta activity in the Placebo group than in all the other groups. No other sites showed this effect during eyes open. This effect is illustrated in Figure 32.

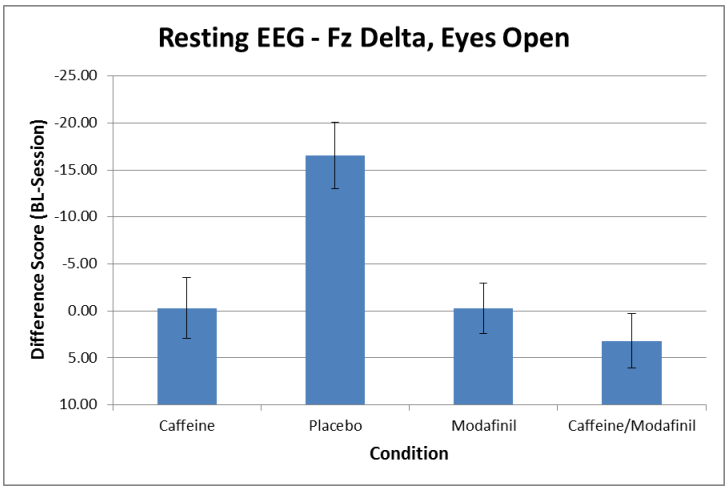

Figure 32. Condition effect during eyes open in the delta band at site Pz.

A session main effect during eyes open occurred at site Cz ($F(4, 44) = 2.641$, $p = .016$, $\eta_p^2 = .194$), but post hoc analyses did not show any statistically-significant differences between any of the sessions. The lowest amount of delta activity occurred at the 0500 session, and the highest amount occurred at the 1400 session, but the variance was large for all sessions.

Analysis of the delta band during eyes closed did not show an interaction between condition and session or a main effect for condition at any of the electrode sites. However, a main effect for session occurred at site Pz ($F(4,48) = 7.687$, $p < .001$, $\eta_p^2 = .390$), with post hoc analyses showing less delta activity during the 0200 session than during any of the other sessions (all p-values < .003). This effect is shown in Figure 33.

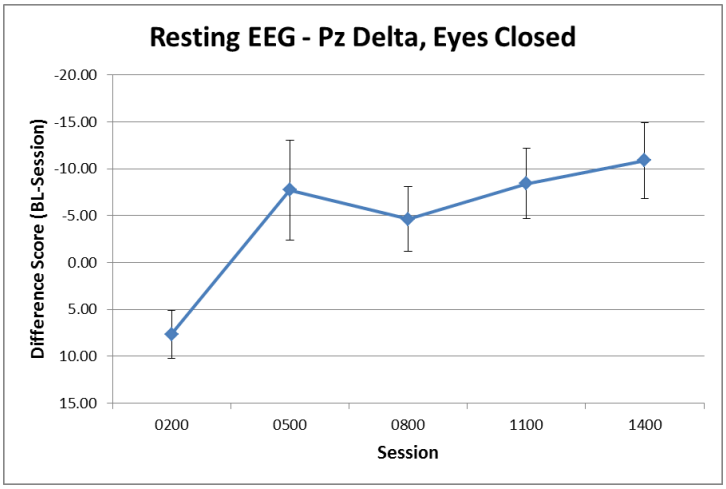

Figure 33. Session effect during eyes closed for the delta band at site Pz.

The analysis of the *theta band* during eyes open did not show any interactions or main effect for condition at any of the electrode sites. However, at site Pz, a session main effect occurred ($F(4,44) = 2.711$, $p = .042$, , $\eta_p^2 = .198$), with post hoc analysis showing less theta activity at the 0200 session than at the 0800 session ($p = .047$). This effect is shown in Figure 34.

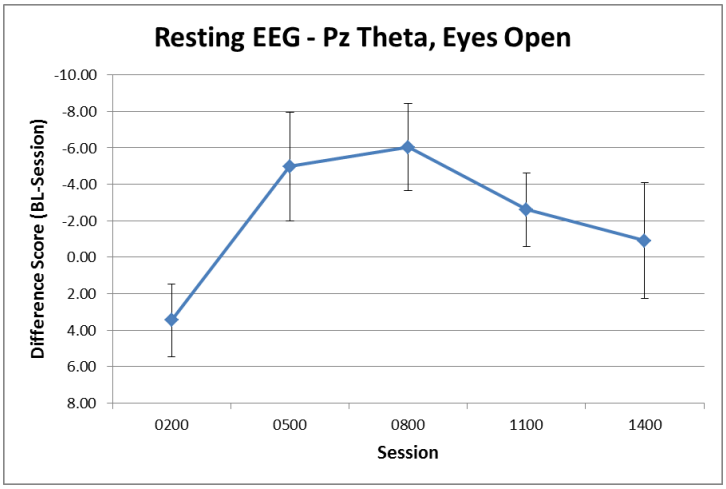

Figure 34. Session effect during eyes open for the theta band at site Pz.

Analysis of the theta band during eyes closed did not show an interaction between condition and session or main effects for condition and session at any of the electrode sites.

The analysis of the *alpha band* during eyes open revealed a significant interaction between condition and session at sites Fz ($F(12,44) = 2.240$, $p = .026$, $\eta_p^2 = .379$), Cz ($F(12,44) = 2.248$, $p = .025$, $\eta_p^2 = .380$), and Pz ($F(12,44) = 3.635$, $p = .001$, $\eta_p^2 = .498$). Follow-up analyses indicated differences among the sessions at site Fz for the Placebo group, with more alpha activity during the 0200 session than at the 0800 session ($p = .051$) and a tendency for more activity during the 0200 session than during the 1100 session ($p = .071$). This effect also occurred in the Modafinil group with more alpha activity at the 0200 session than at the 0800 session ($p = .033$). When

comparing the conditions at each session, analyses indicated more alpha activity at site Pz in the Modafinil group than in the Caffeine group at the 0200 session (p = .006), and less alpha activity at site Pz in the Caffeine/Modafinil group than in the Placebo group at the 1100 session (p = .049). These effects are illustrated in Figure 35.

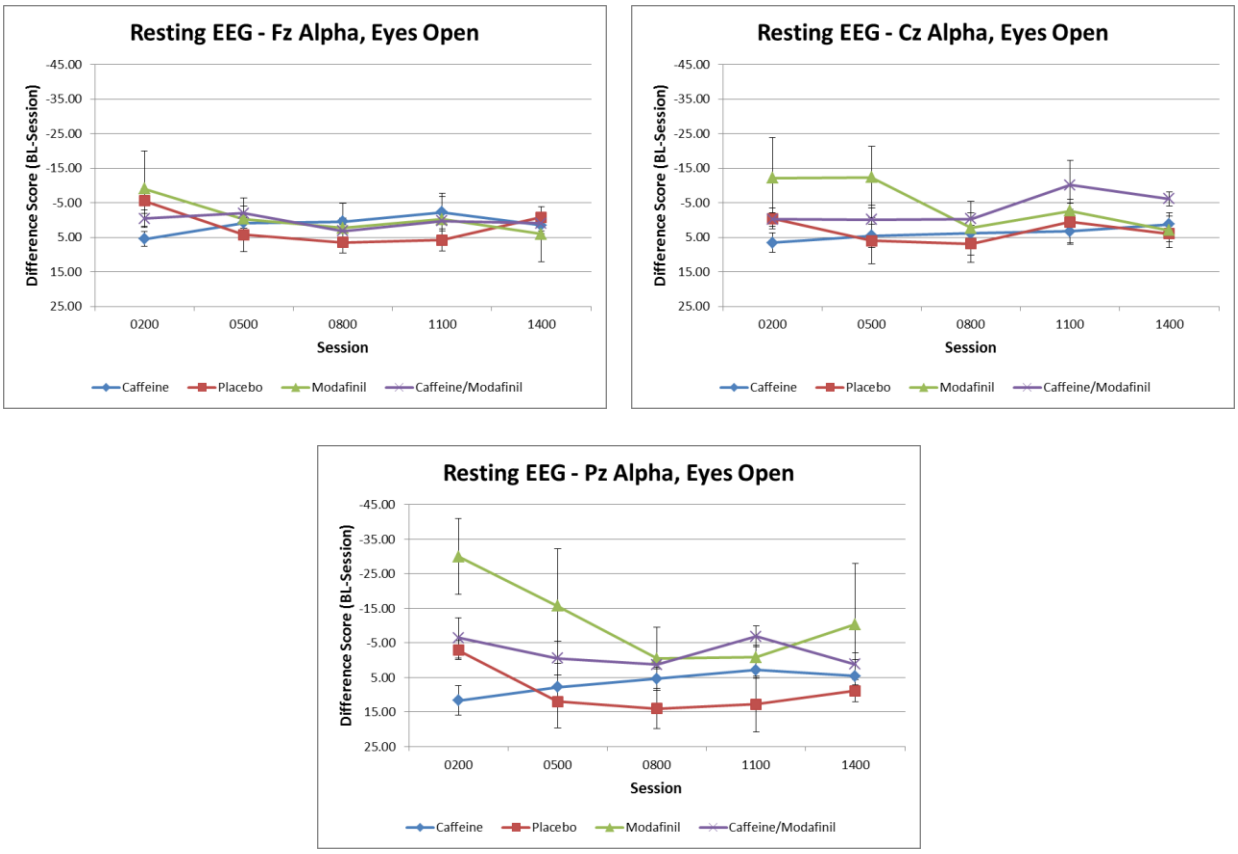

Figure 35. Condition by session interaction during eyes open for the alpha band at all three electrode sites.

The only main effect which occurred was for condition was at site Pz ($F(3,11) = 5.746$, $p = .013$, $\eta_p^2 = .610$). Post hoc analyses showed more alpha activity in the Modafinil group than in the Placebo group (p = .029). This effect is shown in Figure 36.

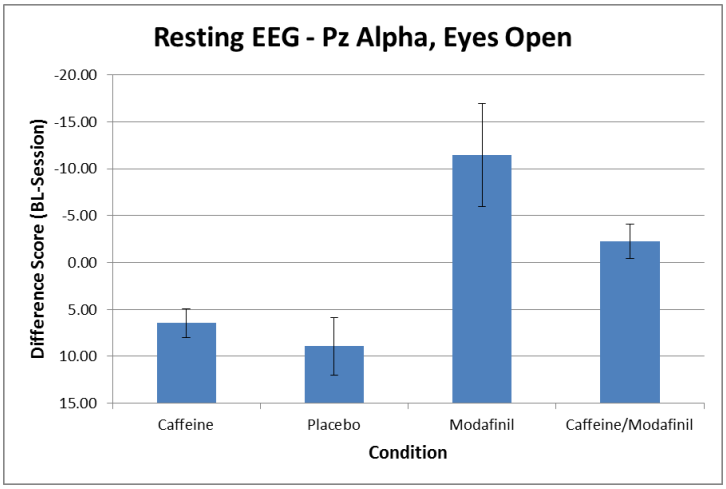

Figure 36. Condition main effect during eyes open for the alpha band at site Pz.

Main effects for session occurred at sites Fz ($F(4,44) = 3.431$, $p = .016$, $\eta_p^2 = .238$), Cz ($F(4,44) = 3.076$, $p = .026$, $\eta_p^2 = .219$), and Pz ($F(4,44) = 6.568$, $p < .001$, $\eta_p^2 = .374$). The only statistically significant difference among the sessions occurred at site Pz, with more alpha activity at the 0200 session than at the 0800 session ($p = .016$). This effect is shown in Figure 37.

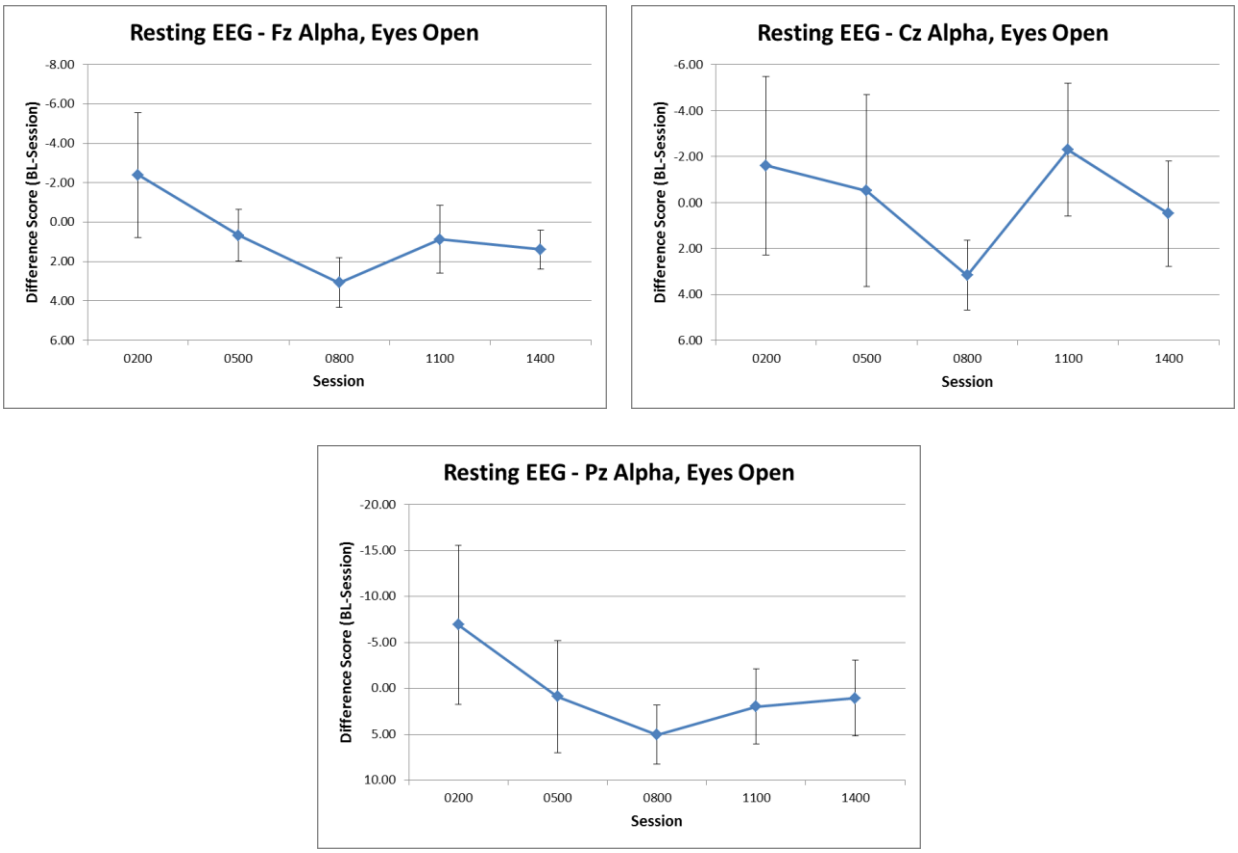

Figure 37. Main effect for session during eyes open for the alpha band at all three electrode sites.

Analysis of the alpha band during eyes closed did not show an interaction between condition and session or main effect for condition. However, a main effect for session occurred at electrode site Pz ($F(4,48) = 2.551$ $p = .051$, $\eta_p^2 = .175$). Post hoc analyses did not show any statistically-significant differences among the sessions ($p > 05$).

The analysis of the *beta band* did not show any significant interactions or main effects for any of the electrode sites.

To analyze the relationship between fast and slow brain activity, the *slow-to-fast ratio* was calculated using the formula ((theta+alpha)/beta). Baseline correction was calculated with this ratio as with the other data. No interaction between condition and session or main effect for condition occurred. However, a main effect for session occurred during eyes open at site Cz ($F(4,44) = 2.641$, $p = .046$, $\eta_p^2 = .194$), but post hoc analyses did not show any effects between sessions. A session main effect occurred during eyes closed at site Pz ($F(4,48) = 3.233$, $p = .020$, $\eta_p^2 = .212$). Post hoc analysis showed less slow-to-fast activity at session 1100 than at session 0800 ($p = .044$). This effect is shown in Figure 38.

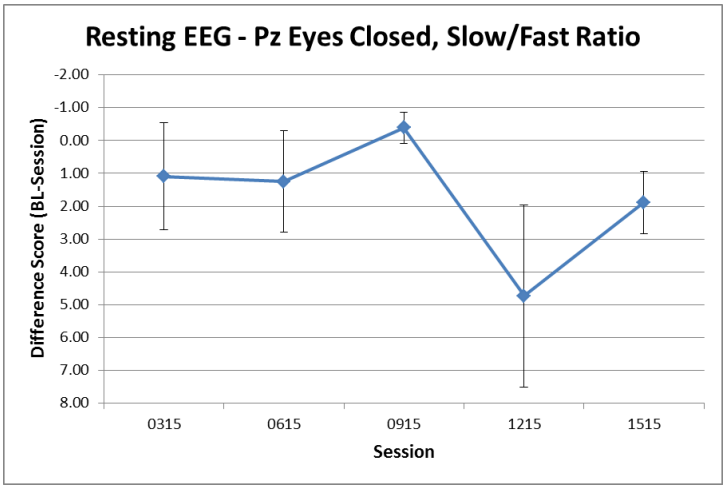

Figure 38. Session main effect for slow/fast ratio during eyes closed at site Pz.

3.2.3.2 Vital signs (temperature, heart rate and blood pressure) were measured at the end of each test session in order to determine any differences which may occur across time within each drug condition. Blood pressure readings were converted to mean arterial pressure (MAP) using the formula ((Systolic pressure) + (2*Diastolic pressure))/3. No interaction between condition and session occurred nor was there a main effect for condition for any of the measures. However, a significant session effect occurred for heart rate ($F(4,56) = 3.212$, $p = .019$, $\eta_p^2 = .187$). Follow-up analyses revealed a tendency for higher heart rate at the 0500 session than at the 0800 session ($p = .067$). The effects are illustrated in Figure 39.

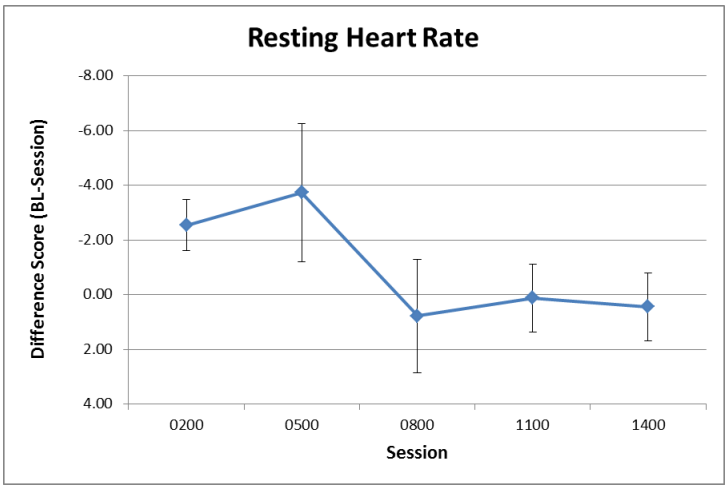

Figure 39. Session main effect for heart rate.

3.2.4 Polysomnography. Analyses of the polysomnography data during each sleep period were made for each of the following variables: total sleep time; sleep latency (minutes to first epoch of stage N1); rapid eye movement sleep (REM); latency (minutes to first epoch of REM sleep); wake after sleep onset; sleep efficiency (number of minutes asleep/number of minutes in bed); percent stage N1; percent stage N2; percent stage N3; and percent stage REM. Due to technical difficulties, two participants' data were not available for analysis. The numbers of people in each group for this data set are 4 in the Caffeine group, 4 in the Placebo group, 3 in the Modafinil group, and 5 in the Caffeine/Modafinil group. The data were converted to difference from baseline as with the other data sets. There were only two nights of data; therefore, the analysis was a one-way between-groups ANOVA.

The only significant effect was for percent stage REM ($F(3,12) = 3.770$, $p = .041$, $\eta_p^2 = .485$). Follow-up analysis revealed a lower percentage of REM sleep in the Caffeine/Modafinil group than in the Placebo group ($p = .050$). Figure 40 illustrates this effect.

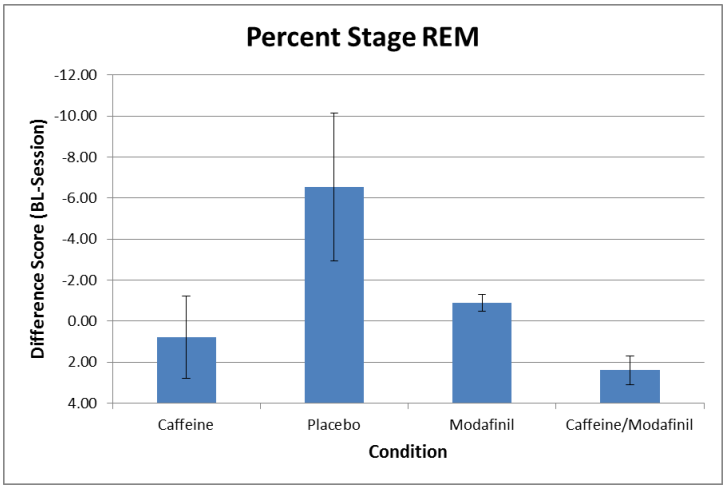

Figure 40. Condition effects of Percent Stage REM.

3.2.5 Exercise assessments. During the 2-mile treadmill walk, participants' resting heart rate and blood pressure were obtained immediately before exercise, both sitting and standing, to establish a baseline. Heart rate was recorded continuously throughout the treadmill walk and was subsequently analyzed over time. In addition, blood pressure and heart rate were collected from a wrist-worn monitor every 3 minutes while walking on the treadmill to assess the stimulants' impact on performance. Following each physiological measurement, participants rated their perceived exertion on a scale of 0 (nothing at all) to 10 (maximal exertion) using the Rating of Perceived Exertion (RPE) Scale. Immediately following the completion of the 2-mile walk, participants' heart rate and blood pressure were measured while sitting, and every 5 minutes for 15 minutes following the walk. Difference scores between baseline and treatment day were calculated for heart rate and blood pressure. The analysis for each of these measures is discussed separately.

3.2.5.1 A one-way ANOVA of the *sitting pre-exercise heart rate* difference score revealed no differences among the groups, however, the one-way ANOVA of the *standing pre-exercise heart rate* showed a condition main effect ($F(3,14) = 5.722$. $p = .009$, $\eta_p^2 = .551$). Post hoc analysis indicated lower heart rates in the Caffeine ($p = .016$) and Caffeine/Modafinil ($p = .042$) groups than in the Placebo group. Figure 41 shows this difference.

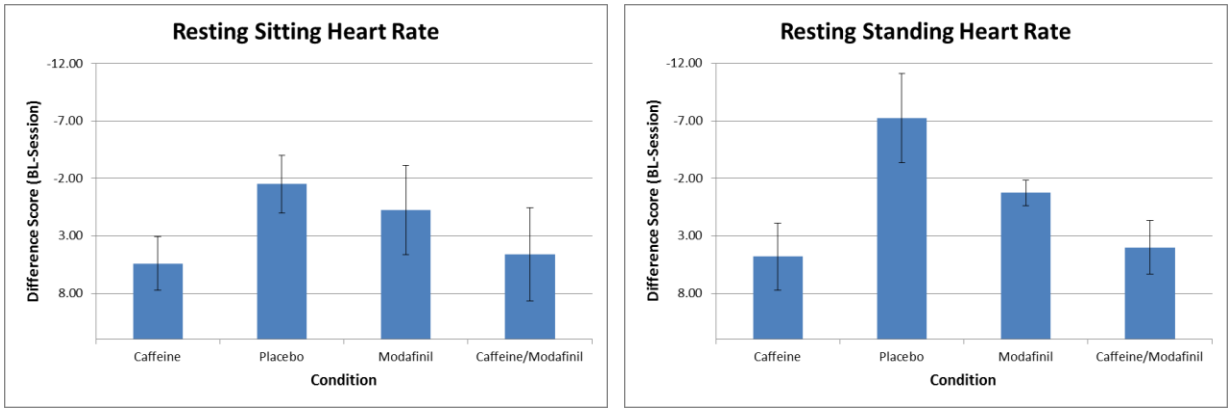

Figure 41. Resting heart rate prior to exercise by condition.

Heart rate and blood pressure stabilize within the first 10 minutes of exercise, therefore, only the first 11 minutes of the heart rate data were analyzed. These first 11 minutes of heart rate were calculated from the program which recorded the EKG signal while the participants were walking on the treadmill. Data were reduced by selecting the calculated heart rate every 500msec. These data were then averaged every 30 seconds. Due to technical difficulties in obtaining an accurate EKG signal while participants were walking on the treadmill, only a subset of data was available for statistical analysis. The number of people in each group with clean signals was 4 for the Caffeine group, 2 for the Placebo group, 2 for the Modafinil group, and 3 for the Caffeine/Modafinil group. The ANOVA for this data set did not show any differences among the conditions or time, or interactions between condition and time. Figure 42 illustrates the heart rate during the first 11 minutes on the treadmill for each condition.

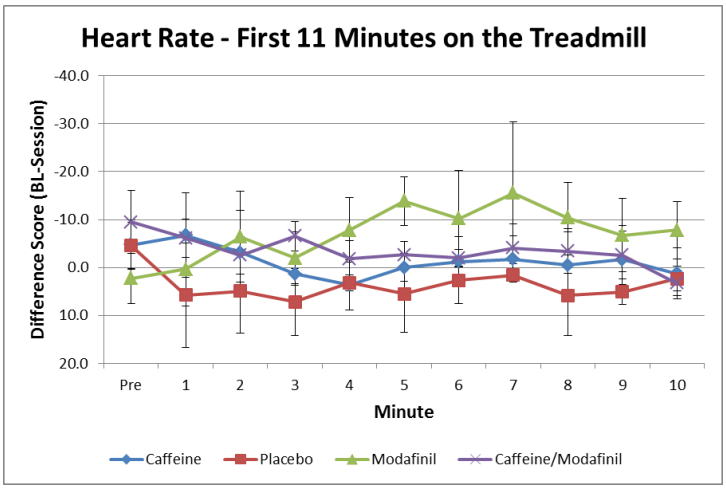

Figure 42. Heart rate during the first 11 minutes on the treadmill for each condition.

3.2.5.2 Blood pressure readings were converted to mean arterial pressure (MAP) using the formula ((systolic pressure) + (2*diastolic pressure))/3. Pre-treadmill readings both sitting and standing were analyzed separately with a one-way ANOVA to determine differences in MAP among the conditions. There were no statistically-significant differences among the groups for either the sitting or standing MAP measurements ($p > .05$). MAP measurements obtained during the treadmill walk showed no differences among the groups ($p > .05$).

3.2.5.3 A one-way ANOVA of the *RPE Scale* difference score from the ratings during the treadmill walk did not show any differences among the groups ($p > .05$). Figure 43 shows the responses for the groups during the first 15 minutes on the treadmill.

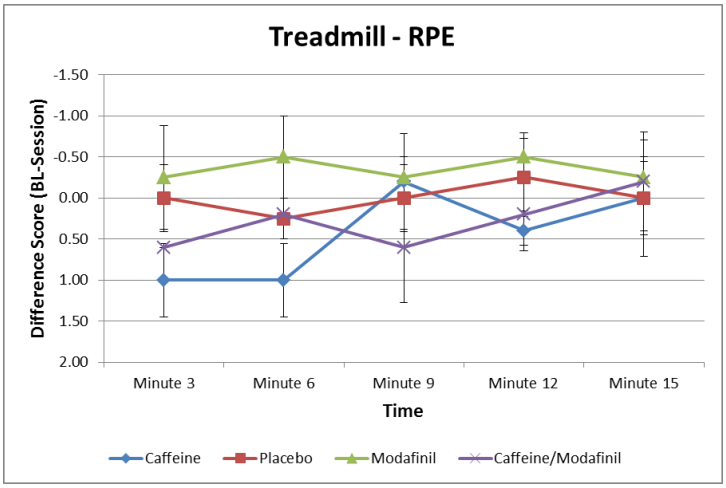

Figure 43. Treadmill RPE score by condition for the first 15 minutes

3.3 Discussion

The purpose of the present study was to investigate the safety and performance effects, either beneficial or harmful, which may occur if caffeine is consumed with modafinil. A variety of

data from research participants were collected through 37 hours of continuous wakefulness during which modafinil, caffeine, or a combination of modafinil and caffeine was consumed. Participants were assigned to one of four groups, either modafinil (200mg), caffeine (200mg), modafinil combined with caffeine, or placebo. Research volunteers engaged in submaximal exercise once during baseline and once during the continuous wakefulness period, 1 hour after administration of the drug (or placebo). Cognitive performance, subjective mood, and physiological parameters were measured at baseline and then during 37 hours of continuous wakefulness. Subjective symptoms of potential side effects were also recorded from a questionnaire completed at the end of each testing session.

Due to various circumstances, the number of participants who successfully completed the study was low, resulting in only 4-5 participants in each group. The small number of participants combined with high variance led to low power in many cases. However, in order to show the magnitude of the effects, partial eta-squared (η_p^2) is reported with each F statistic and *p* value.

3.3.1 Effects of treatment and continuous wakefulness on cognitive performance. As expected, individuals kept awake for 37 hours showed decrements in performance on almost all of the cognitive assessments in this study. Generally, reaction time slowed as time awake progressed. This effect was shown in the PVT and the Go/No-Go tests. Accuracy was also affected over time, with poorer performance as time awake increased, reflected in the performance on both the flight simulator and the Go/No-Go test. Risk-taking behavior increased as a function of time awake as shown in the performance on the BART. Modafinil treatment conditions were associated with improved reaction time and performance in the PVT and the Go/No-Go test, with the Modafinil and Caffeine/Modafinil groups showing faster RTs than the Placebo and Caffeine groups. The most salient effect was in response inhibition as measured by the Go/No-Go task, with individuals in both the Modafinil and Caffeine/Modafinil groups showing similar number correct and incorrect responses across the sessions as before sleep deprivation (baseline measures). From these results, there was no consistent benefit or disadvantage to combining modafinil with caffeine on any performance measures above that seen with modafinil alone.

3.3.2 Effects of treatment and continuous wakefulness on subjective mood and side effects. Subjective measures of mood indicated a decrease in alertness and an increase in fatigue as time awake increased. These effects were consistent in the POMS and VAS measurements of these factors. Treatment effects were most noticeable during the circadian nadir where sleepiness levels stayed higher for those receiving modafinil or a combination of modafinil and caffeine compared to those receiving placebo. This effect was most obvious when all factors from the POMS were combined into the Total Mood Disturbance score, with those in the Placebo group showing higher levels of mood disturbance than was seen in any of the treatment groups.

Subjective measures of side effects were not analyzed statistically, however, the number of people reporting incidences such as tremor, headache, or nausea were few. The highest number of complaints occurred in those individuals who were in the Placebo group or the groups who received caffeine, whether in combination with modafinil or alone. Based on these subjective reports, combining modafinil with caffeine does not appear to increase side effects in this select group of individuals.

3.3.3 Effects of treatment and continuous wakefulness on physiological parameters. As with the other parameters, the physiological measurements indicated increased sleepiness as time awake increased. The resting EEG showed increased delta activity and decreased alpha activity as time awake progressed. Modafinil and the combination of caffeine and modafinil delayed this progression from alpha activity to the slower delta activity, indicating an ability to stay alert better with the treatment than without it or with only caffeine. However, oculometrics obtained from the PMI FIT were affected by increased time awake and circadian phase, but the treatment did not change the pattern of these measurements. Vital signs also were not affected by any of the treatments. Only heart rate decreased across time.

Analysis of sleep architecture during baseline sleep and recovery sleep showed an increase in REM sleep during the recovery night of people in the Placebo group compared to the people in the Caffeine/Modafinil group. There is no indication in published studies that modafinil affects sleep architecture. This effect may be due to either spurious statistical results or the combined effects of modafinil and caffeine may have an effect on REM sleep. Given that the recovery REM percentage is similar to the baseline percentage, it is doubtful that the combination of these two substances has substantial effects on REM sleep; however, further study may be useful to address this question.

3.3.4 Effects of treatment during exercise. No significant effects were seen among the treatment conditions during the 2-mile treadmill walk. While there was a statistically-significant effect among the conditions for the resting heart rate immediately after the participant stood up, the participants in the groups with caffeine (caffeine alone or in combination with modafinil) had lower heart rates than the participants in the other groups. This may have been due to a protective effect from the caffeine. When one stands up, blood flows to the lower extremities, partly due to the fact that blood flows to any muscle being worked and partly due to the effects of gravity. Thus, when standing, the heart beats faster to work against gravity and get the blood pumped through the body and back to the heart. Caffeine may have allowed greater peripheral vasoconstriction which assisted in maintaining central blood volume and reduced the need to increase heart rate to maintain blood pressure.

4.0 CONCLUSIONS

The present study sought to determine the effects of combing two alertness aids, caffeine and modafinil, on cognitive and physical measures. The effects of the treatments replicated what is typically reported in the literature; modafinil, whether alone or in combination with caffeine, increased alertness and performance across the 37-hour period of continuous wakefulness. When combined with caffeine, the effects were the same for most of the cognitive measures. The subjective side effects did not increase with the combination of the two alertness aids, nor were the vital sign measurements changed due to the combination of the drugs, including those vital sign measurements taken while walking on the treadmill. In this select group of study participants, the combination of caffeine with modafinil does not appear to improve or inhibit performance above that with modafinil alone.

This group of participants was young and in good physical condition. Combining these two drugs in an older, less fit group may have shown different effects, so further study is needed before concluding that no problems will occur in people with different characteristics than those in this sample. Larger doses of caffeine may have also produced different effects. The dose chosen for this study was 200mg in low-caffeine users. Higher doses can produce more physiological effects such as high heart rate. Investigations using higher caffeine doses combined with the standard dose of modafinil (200mg) may produce different results than shown in this study. Before concluding that any dose of caffeine combined with modafinil will not produce unwanted side effects, investigation with various dosage combinations is warranted.

The level of exercise investigated in this study was submaximal. Walking 2 miles at 3 mph with a 30-lb pack is not significantly stressful for most physically-fit individuals. A more strenuous exercise which increased workload and effort may have produced different effects as well. Further study with more strenuous exercise may have produced different effects than shown in this study.

The number of people in each group was small in this study which may have led to non-significant statistical results. However, the effect sizes in most of the analyses were small. In order to obtain a statistically-significant difference among the groups, an increase in the number of people per group would have to have been over 40 in many cases.

In conclusion, based on the data obtained in the present study, the combination of modafinil and caffeine does not lead to better cognitive performance than modafinil alone. The combination also does not produce higher subjective side effects or concerns with vital signs than with either substance alone.

5.0 REFERENCES

American College of Sports Medicine. (2010). American College of Sports Medicine (ACSM) Guidelines for Exercise Testing and Prescription. , 8th edition, Lippincott Williams & Wilkins.

Babkoff, H. & Krueger, G.P. (1992). Use of stimulants to ameliorate the effects of sleep loss during sustained performance. *Military Psychology, 4*, 191-205.

Baranski, J.V., Cian, C., Esquivié, D., Pigeau, R.A., & Raphel, C. (1998). Modafinil during 64 hr of sleep deprivation: Dose-related effects on fatigue, alertness, and cognitive performance. *Military Psychology, 10*, 173-193.

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*, 323-332.

Caldwell, J.A. (2001). The impact of fatigue in air medical and other types of operations: A review of fatigue facts and potential countermeasures. *Air Medical Journal, 20*, 25-32.

Caruso, C.C. (2014). Negative impacts of shiftwork and long work hours. *Rehabilitation Nursing, 39*(1), 16-25.

Costa, P. T. & McCrae, R. R. (1992). *Revised NEO Personality Inventory (NEO-PI-R) and NEO Five Factor Inventory (NEO-FFI) Manual.* Odessa, FL: Psychological Assessment Resources.

Cuddy, J.S., Reinert, A.R., Hansen, K.C., & Ruby, B.C. (2008). Effects of modafinil and sleep loss on physiological parameters. *Military Medicine, 173*, 1092-1097.

Czeisler, C.A., Walsh, J.K., Roth, T., Hughes R.J., Wright, K.P., Kingsbury, L., Arora, S., Schwartz, J.R., Niebler, G.E., & Dinges, D.F. (2005). Modafinil for excessive sleepiness associated with shift-work sleep disorder. *New England Journal of Medicine, 353*, 476-486.

Darwish, M., Kirby, M., D'Andrea, D.M., Yang, R., Hellriegel, E.T., & Robertson, P. (2010). Pharmacokinetics of armodafinil and modafinil after single and multiple doses in patients with excessive sleepiness associated with treated obstructive sleep apnea: A randomized, open-label, crossover study. *Clinical Therapeutics, 32*, 2074-2087.

Emonson, D.L. & Vanderbeek, R.D. (1995). The use of amphetamines in U.S. Air Force tactical operations during Desert Shield and Storm. *Aviation, Space, and Environmental Medicine, 66*, 260-263.

Gillingham, R.L., Keefe, A.A., & Tikuisis, P. (2004). Acute caffeine intake before and after fatiguing exercise improves target shooting engagement time. *Aviation, Space, and Environmental Medicine, 75*, 865-871.

Gore, R.K., Webb, T.S., & Hermes, E.D.A. (2010). Fatigue and stimulant use in military fighter aircrew during combat operations. *Aviation, Space and Environmental Medicine, 81*, 719-727.

Horne, J. A., & Östberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International Journal of Chronobiology, 4*, 97-110.

Horne, J.A. & Reyner, L.A. (1996). Counteracting driver sleepiness: Effects of napping, caffeine, and placebo. *Psychophysiology, 33*, 306-309.

Jacobs, I. & Bell, D.G. (2004). Effects of acute modafinil ingestion on exercise time to exhaustion. *Medicine and Science in Sports and Exercise, 36*, 1078-1082.

Kamimori, G.H., Karyekar, C.S., Otterstetter, R., Cox, D.S., Balkin, T.J., Belenky, G.L., & Eddington, N.D. (2002). The rate of absorption and relative bioavailbility of caffeine administered in chewing gum versus capsules to normal healthy volunteers. *International journal of Pharmaceutics, 234*; 159-167.

Killgore, W.D.S., Grugle, N.L., Killgore, D.B., Leavitt, B.P., Watlington, G.I., McNair, S., & Balkin, T.J. (2008). Restoration of risk-propensity during sleep deprivation: Caffeine, dextroamphetamine, and modafinil. *Aviation, Space, and Environmental Medicine, 79*, 867-874.

Lejuez, C.W., Read, J.P., Kahler, C.W., Richards, J.B., Ramsey, S.E., Stuart, G.L., Strong, D.R., & Brown, R.A. (2002). Evaluation of a behavioral measure of risk taking: The Balloon Analogue Risk Task (BART). *Journal of Experimental Psychology: Applied, 8*, 75-84.

Lieberman, H.R.,Stavinoha, T.B., McGraw, S.M., White, A., Hadden, L.S., & Marriott, B.P. (2012). Caffeine use among active duty US Army soldiers. *Journal of the Academy of Nutrition and Dietetics, 112*, 902-912.

Lieberman, H.R., Stavinoha, T.B., White, A., Hadden, L.S., & Marriott, B.P. (2010). Use of dietary supplements among active-duty US Army soldiers. *American Journal of Clinical Nutrition, 92*, 985-995.

Lorist, M.M., Snel, J., & Kok, A. (1994). Influence of caffeine on information processing stages in well rested and fatigued subjects. *Psychopharmacology, 113*, 411-421.

McNair, D.M., Lorr, M. & Droppleman, L.F. (1981). *Manual for the profile of mood states*. San Diego: Educational and Industrial Testing Service.

Penetar, D., McCann, U., Thorne, D., Kamimori, G., Galinski, C., Sing, H., Thomas, M., & Belenky, G. (1993). Caffeine reversal of sleep deprivation effects on alertness and mood. *Psychopharmacology, 112*, 359-365.

Philip, P., Taillard, J., More, N., Delord, S., Valtat, C., Sagaspe, P., & Bioulac, B. (2006). The effects of coffee and napping on nighttime highway driving. *Annals of Internal Medicine, 144*, 785-791.

Rosekind, M.R., Gregory, B.S., Mallis, M.M., Brandt, S.L., Seal, B., & Lerner, D. (2010). The cost of poor sleep: Workplace productivity loss and associated costs. *Journal of Occupational and Environmental Medicine, 52*(1), 91-98.

Wesensten, N.J., Killgore, W.D., & Balkin, T.J. (2005). Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation. *Journal of Sleep Research, 14*, 255-266.

White, T.L., Lejuez, C.W., & de Wit, H. (2008). Test-retest characteristics of the Balloon Analogue Risk Task (BART). *Experimental and Clinical Psychopharmacology, 16*, 565-570.

SYMBOLS

η_p^2	Partial eta squared

ABBREVIATIONS

FRRT	10% Fastest reciprocal reaction time
SRRT	10% Slowest reciprocal reaction time
AFMSA/SG9	Air Force Medical Support Agency Office of Medical Modernization
BP	Blood pressure
BCA	Body composition assessment
DC	Direct current
DHP	Defense Health Program
ECG	Electrocardiograph
EEG	Electroencephalogram
EMG	Elecotromyogram
EOG	Electrooculogram
FFT	Fast Fourier transformation
FDDTB	Form and Depth Discrimination Test Battery
GC-MS	Gas chromatography-mass spectrometry
HR	Heart rate
HSD	Honestly Significant Difference
Hz	Hertz
MHR	Maximal heart rate
MAP	Mean arterial pressure
Mg	Milligram
MPH	Miles per hour
Msec	Millisecond
NAMRU-D	Naval Medical Research Unit Dayton
OTC	Over the counter
PVT	Psychomotor Vigilance Task
RPE	Rating of Perceived Exertion
RT	Reaction time
RTCE	Reaction time for commission errors
RTCR	Reaction time for correct responses
RRT	Reciprocal reaction time
RMS	Root mean square
SE	Side effects
Sd	Standard deviation
SBP	Systolic blood pressure
TMD	Total Mood Disturbance

ACRONYMS

AFSOC	Air Force Special Operations Command
ANAM®	Automated Neuropsychological Assessment Metrics

ANOVA	Analysis of variance
BART	Balloon Analogue Risk Task
FIT	Fitness Impairment Tester
NEO-PI-R	NEO Personality Inventory Revised
POMS	Profile of Mood States
REM	Rapid eye movement
VAS	Visual Analogue Scale